

TRANSMITTAL LETTER TO THE UNITED STATES
DESIGNATED/ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 U.S.C. 371

1241.18

U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.5)

09/806232

INTERNATIONAL APPLICATION NO.

PCT/JP99/05349

INTERNATIONAL FILING DATE

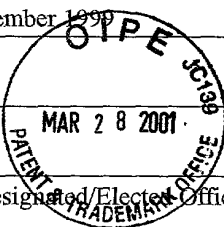
29 September 1999

PRIORITY DATE CLAIMED

29 September 1998

TITLE OF INVENTION

DNAS ENCODING NOVEL POLYPEPTIDES



JCO7 Rec'd PCT/JP 28 MAR 2001

* APPLICANT(S) FOR DO/EO/US

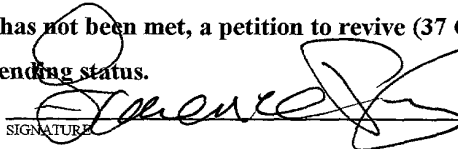
Motoharu Seiki

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the application time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
 - a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☒ has been transmitted by the International Bureau.
 - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
- ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
- ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
 - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☐ have been transmitted by the International Bureau.
 - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
 - d. ☒ have not been made and will not be made.
- ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
- ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
- ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A **FIRST** preliminary amendment.
☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information: Submission of Computer Readable Form; Form PCT/IPEA/409; Form PCT/IB/308; Copy of Published International Application No. WO00/18900; Form PCT/ISA/210.

U.S. APPLICATION NO. (If known, see 37 CFR 1.5) 09/806232		INTERNATIONAL APPLICATION NO PCT/JP99/05349		ATTORNEY'S DOCKET NUMBER 1241.18	
17. <input checked="" type="checkbox"/> The following fees are submitted: Basic National Fee (37 CFR 1.492(a)(1)-(5): Search Report has been prepared by the EP or JPO \$860.00 International preliminary examination fee paid to USPTO (37 CFR 1.492(a)(1)) \$690.00 No international preliminary examination fee paid to USPTO (37 CFR 1.492 (a)(1)) but international search fee paid to USPTO (37 CFR 1.492(a)(2)) \$710.00 Neither international preliminary examination fee (37 CFR 1.492(a)(1)) nor international search fee (37 CFR 1.492(a)(2)) paid to USPTO \$1,000.00 International preliminary examination fee paid to USPTO (37 CFR 1.492 (a)(4)) and all claims satisfied provisions of PCT Article 33(1)-(4) \$100.00 ENTER APPROPRIATE BASIC FEE AMOUNT =				CALCULATIONS	PTO USE ONLY
Surcharge of \$130.00 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				\$	
Claims	Number Filed	Number Extra	Rate		
Total Claims	114 - 20 =	94	X \$18.00	\$1692.00	
Independent Claims	6 - 3 =	3	X \$80.00	\$240.00	
Multiple dependent claim(s) (if applicable)			+ \$270.00	\$270.00	
TOTAL OF ABOVE CALCULATIONS =				\$3062.00	
<input checked="" type="checkbox"/> Applicant claims small entity status. See 37 C.F.R. 1.27. The fees indicated above are reduced by 1/2.				\$1531.00	
SUBTOTAL =				\$1531.00	
Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				\$	
TOTAL NATIONAL FEE =				\$1531.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property +				\$	
TOTAL FEES ENCLOSED =				\$1531.00	
				Amount to be:	
				refunded	\$
				charged	\$
a. <input checked="" type="checkbox"/> A check in the amount of \$ 1531.00 to cover the above fees is enclosed. b. <input type="checkbox"/> Please charge my Deposit Account No. _____ in the amount of \$ _____ to cover the above fees. A duplicate copy of this sheet is enclosed. c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 06-1205. A duplicate copy of this sheet is enclosed.					
NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status. SEND ALL CORRESPONDENCE TO:					
Lawrence S. Perry FITZPATRICK, CELLA, HARPER & SCINTO 30 Rockefeller Plaza New York, NY 10112 Tel: (212) 218-2100 Fax: (212) 218-2200			SIGNATURE  _____ Lawrence S. Perry NAME 31,865 REGISTRATION NUMBER		

1241.18

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:)
Motoharu Seiki) : Examiner: Not Yet Assigned
Application No.: N/Y/A) : Group Art Unit: N/Y/A
Filed: Currently herewith) :
For: DNAS ENCODING NOVEL) :
POLYPEPTIDES) : March 27, 2001

Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Sir:

Prior to action on the merits, please amend the
above-identified application as follows:

IN THE CLAIMS:

Please amend Claims 13, 18-21, 25, 26, 29, 30 and
32. A marked up copy of Claims 13, 18-21, 25, 26, 29, 30 and
32, showing the changes made thereto, is attached.

13. (Amended) A recombinant DNA that is obtained
by integrating the DNA of any one of claims 11 or 12 into a
vector.

18. (Amended) An oligonucleotide selected from an oligonucleotide having a nucleotide sequence identical with a nucleotide sequence consisting of consecutive 5 to 60 bases of the DNA of claim 9; an oligonucleotide having a nucleotide sequence complementary to the nucleotide sequence of said oligonucleotide; or an oligonucleotide derivative of any one of the above oligonucleotides.

19. (Amended) An oligonucleotide selected from an oligonucleotide having a nucleotide sequence identical with a nucleotide sequence consisting of consecutive 5 to 60 bases of the DNA of claim 10; an oligonucleotide having a nucleotide sequence complementary to the nucleotide sequence of said oligonucleotide; or an oligonucleotide derivative of any one of the above oligonucleotides.

20. (Amended) A method of detecting an mRNA encoding the polypeptide of any one of claims 1 to 8 using an oligonucleotide selected from an oligonucleotide having a nucleotide sequence identical with a nucleotide sequence consisting of consecutive 5 to 60 bases of the DNA of claim 9; an oligonucleotide having a nucleotide sequence complementary to the nucleotide sequence of said oligonucleotide; or an oligonucleotide derivative of any one of the above oligonucleotides.

21. (Amended) A method of inhibiting expression of the polypeptide of any one of claims 1 to 8 using an oligonucleotide selected from an oligonucleotide having a nucleotide sequence identical with a nucleotide sequence consisting of consecutive 5 to 60 bases of the DNA of claim 9; an oligonucleotide having a nucleotide sequence complementary to the nucleotide sequence of said oligonucleotide; or an oligonucleotide derivative of any one of the above oligonucleotides.

25. (Amended) A diagnostic agent, therapeutic agent or prophylactic agent for arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, wounds, corneal ulcer, tissue injury or inflammations associated with infiltration of leukocytes, wherein said agent comprises the DNA of claim 9.

26. (Amended) A diagnostic agent, therapeutic agent or prophylactic agent for arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ

transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, wounds, corneal ulcer, tissue injury, inflammations associated with infiltration of leukocytes, brain disorders at the time of cerebral apoplexy, Alzheimer's disease, dementia, multiple sclerosis, Parkinson's disease or brain tumor, wherein said agent comprises the DNA of claim 10.

29. (Amended) A vector for gene therapy for treating arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, wounds, corneal ulcer, tissue injury or inflammations associated with infiltration of leukocytes, wherein said vector is obtained by integrating the oligonucleotide of claim 18 into a vector.

30. (Amended) A vector for gene therapy for treating arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, wounds, corneal ulcer, tissue injury,

inflammations associated with infiltration of leukocytes, brain disorders at the time of cerebral apoplexy, Alzheimer's disease, dementia, multiple sclerosis, Parkinson's disease or brain tumor, wherein said vector is obtained by integrating the oligonucleotide of claim 19 into a vector.

32. (Amended) The method of claim 31, wherein said compound that regulates the expression of a gene is detected by determining the amount of mRNA encoding the polypeptide.

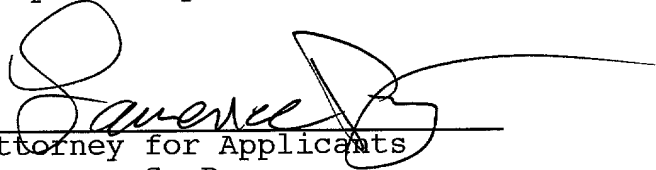
REMARKS

Claims 13, 18-21, 25, 26, 29, 30 and 32 have been amended to correct their dependency and conformity with accepted U.S. practice. No new matter has been added.

Entry hereof is earnestly solicited.

Applicants' undersigned attorney may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our below listed address.

Respectfully submitted,


Attorney for Applicants
Lawrence S. Perry
Registration No. 31,865

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New York, New York 10112-3801
Facsimile: (212) 218-2200

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VERSION WITH MARKINGS SHOWING CHANGES MADE TO CLAIMS

13. (Amended) A recombinant DNA that is obtained by integrating the DNA of any one of claims [9 to]11 or 12 into a vector.

18. (Amended) An oligonucleotide selected [form] from an oligonucleotide having a nucleotide sequence identical with a nucleotide sequence consisting of consecutive 5 to 60 bases of the DNA of claim 9 [or 11]; an oligonucleotide having a nucleotide sequence complementary to the nucleotide sequence of said oligonucleotide; or an oligonucleotide derivative of any one of the above oligonucleotides.

19. (Amended) An oligonucleotide selected form an oligonucleotide having a nucleotide sequence identical with a nucleotide sequence consisting of consecutive 5 to 60 bases of the DNA of claim 10 [or 12]; an oligonucleotide having a nucleotide sequence complementary to the nucleotide sequence of said oligonucleotide; or an oligonucleotide derivative of any one of the above oligonucleotides.

20. (Amended) A method of detecting an mRNA encoding the polypeptide of any one of claims 1 to 8 using [the] an oligonucleotide [of claim 18 or 19] selected from an oligonucleotide having a nucleotide sequence identical with a nucleotide sequence consisting of consecutive 5 to 60 bases of the DNA of claim 9; an oligonucleotide having a nucleotide sequence complementary to the nucleotide sequence of said oligonucleotide; or an oligonucleotide derivative of any one of the above oligonucleotides.

21. (Amended) A method of inhibiting expression of the polypeptide of any one of claims 1 to 8 using [the] an oligonucleotide [of claim 18 or 19] selected from an oligonucleotide having a nucleotide sequence identical with a nucleotide sequence consisting of consecutive 5 to 60 bases of the DNA of claim 9; an oligonucleotide having a nucleotide sequence complementary to the nucleotide sequence of said oligonucleotide; or an oligonucleotide derivative of any one of the above oligonucleotides.

25. (Amended) A diagnostic agent, therapeutic agent or prophylactic agent for arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis,

arteriosclerosis, leukemia, malignant tumor, wounds, corneal ulcer, tissue injury or inflammations associated with infiltration of leukocytes, wherein said agent comprises the DNA of claim 9 [or 11].

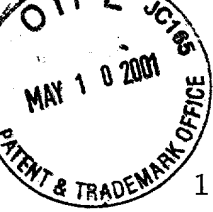
26. (Amended) A diagnostic agent, therapeutic agent or prophylactic agent for arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, wounds, corneal ulcer, tissue injury, inflammations associated with infiltration of leukocytes, brain disorders at the time of cerebral apoplexy, Alzheimer's disease, dementia, multiple sclerosis, Parkinson's disease or brain tumor, wherein said agent comprises the DNA of claim 10 [or 12].

29. (Amended) A vector for gene therapy for treating arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, wounds, corneal ulcer, tissue injury or inflammations associated with infiltration of leukocytes,

wherein said vector is obtained by integrating the [DNA of claim 9 or 11, or the] oligonucleotide of claim 18 into a vector.

30. (Amended) A vector for gene therapy for treating arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, wounds, corneal ulcer, tissue injury, inflammations associated with infiltration of leukocytes, brain disorders at the time of cerebral apoplexy, Alzheimer's disease, dementia, multiple sclerosis, Parkinson's disease or brain tumor, wherein said vector is obtained by integrating the [DNA of claim 10 or 12, or the] oligonucleotide of claim 19 into a vector.

32. (Amended) The method of claim 31, wherein said compound that regulates the expression of a gene is detected by determining the amount of mRNA encoding the polypeptide [of any one of claims 1 to 8].



1241.18

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:)
Motoharu Seiki) : Examiner: Not Yet Assigned
Application No.: 09/806,232) : Group Art Unit: N/Y/A
Filed: March 28, 2001) :
For: DNAS ENCODING NOVEL) :
POLYPEPTIDES) : May 10, 2001

Commissioner for Patents
Washington, D.C. 20231

SUPPLEMENTAL PRELIMINARY AMENDMENT

Sir:

Further to the Preliminary Amendment filed March 28, 2001 and prior to action on the merits, please amend the above-identified application as follows:

IN THE SPECIFICATION

Please substitute the paragraph starting at page 39, line 5 and ending at line 8 with the following replacement paragraph. A marked-up copy of this paragraph, showing the changes made thereto, is attached.

In human, the expression of MT5-MMP was strong in the brain, and its expression was observed in the kidney and pancreas. The results of examination of its site-specific



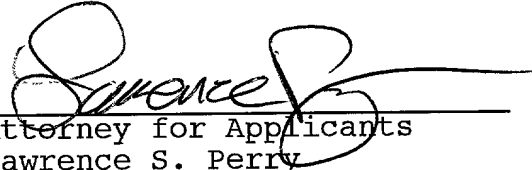
expression in the human brain revealed a characteristic expression in the cerebellum. High expression in the cerebellum was also confirmed in mouse.

REMARKS

The specification has been amended to correct an inadvertent word processing error. Since no new matter has been added, entry hereof is earnestly solicited.

Applicants' undersigned attorney may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our below listed address.

Respectfully submitted,



Attorney for Applicants
Lawrence S. Perry
Registration No. 31,865

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VERSION WITH MARKINGS TO SHOW CHANGES MADE TO SPECIFICATION

The paragraph starting at page 39, line 5 and ending at line 8 has been amended as follows.

In human, the expression of MT5-MMP [also] was strong in the brain, and its expression was observed in the kidney and pancreas. The results of examination of its site-specific expression in the human brain revealed a characteristic expression in the cerebellum. High expression in the cerebellum was also confirmed in mouse.

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09/806232

JCO3'Rec'r PCT/PTO 2 8 MAR 2001

1241.18

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:)
Motoharu Seiki) : Examiner: Not Yet Assigned
Application No.: N/Y/A) : Group Art Unit: N/Y/A
Filed: Currently herewith) :
For: DNAS ENCODING NOVEL) :
POLYPEPTIDES) : March 27, 2001

Commissioner for Patents
Washington, D.C. 20231

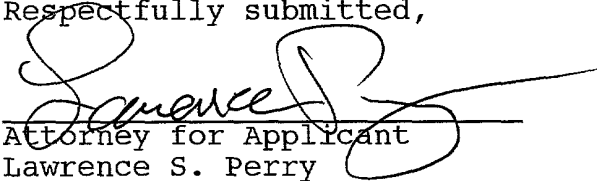
SUBMISSION OF COMPUTER READABLE FORM
UNDER 37 C.F.R. § 1.821(e)

Sir:

Applicants submit herewith a computer readable form under 37 C.F.R. § 1.821(e). The content of the computer readable form and the Sequence Listing filed herewith are the same.

Applicants' undersigned attorney may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our below listed address.

Respectfully submitted,


Attorney for Applicant
Lawrence S. Perry
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09/806252
JC03 Rec'd PCT/PTO 28 MAR 2001

DESCRIPTION

DNAS ENCODING NOVEL POLYPEPTIDES

TECHNICAL FIELD

The present invention relates to novel membrane-type matrix metalloproteinase polypeptides; DNAs encoding the polypeptides; vectors comprising the DNAs; transformants transformed with the vectors; and a method of producing the polypeptides. Furthermore, the present invention relates to a method of searching for inhibitors or activators of the polypeptides using the polypeptides, a part thereof, or microorganisms or animal cells expressing the polypeptides or a part thereof, as well as a method of searching for compounds that regulate the gene expression of the polypeptides.

BACKGROUND ART

A group of enzymes generically termed "matrix metalloproteinases" (hereinafter, abbreviated to MMPs) that have metal ions at the active center are involved in the degradation of extracellular matrix composed of complicated components such as collagens, fibronectin, laminin and proteoglycans.

To date, the following MMPs have been reported: interstitial collagenase (MMP-1), gelatinase A (MMP-2), gelatinase B (MMP-9), stromelysin 1 (MMP-3), matrilysin (MMP-7), neutrophil collagenase (MMP-8), stromelysin 2 (MMP-10), stromelysin 3 (MMP-11), metallo-elastase (MMP-12), collagenase 3 (MMP-13), membrane type 1 MMP (MT1-MMP or MMP-14), membrane type 2 MMP (MT2-MMP or MMP-15), membrane type 3 MMP (MT3-MMP or MMP-16), membrane type 4 MMP (MT4-MMP or MMP-17), etc. (Protein, Nucleic Acid and Enzyme, 42, 2386 (1997)). These MMPs form a family, and each MMP is basically composed of an N-terminal propeptide domain, an active domain to which zinc ions bind, and a hemopexin-like domain. In MMP-7, no hemopexin-like domain is found. Transmembrane-type MMPs have a transmembrane domain and a intracellular domain at the C-terminal of the hemopexin-like domain.

A human MT4-MMP gene has already been reported [Puente, Cancer Research, 56, 944 (1996)]. However, a translation initiation site is not included in the nucleotide sequence of this gene, and this gene was defined as a human MT4-MMP gene simply because it comprises a nucleotide sequence containing MMP-like domains. Thus, it is difficult to consider that this gene encodes the full-length of MT4-MMP.

On the other hand, it is known that production of MT1-MMP is enhanced in patients with arthrosis deformans [Am. J. Pathol., 151, 245 (1997)]; that MMPs are important for the infiltration of leukocytes into tissues that is important in immunological and inflammatory reactions [J. Immunol., 156, 1 (1996)]; that MMP inhibitors prevent hepatitis [Eur. J. Pharmacol., 341, 105 (1998)]; and that MMP inhibitors are effective for treating corneal ulcer [Japanese Journal of Ophthalmology, 102, 270 (1998)].

It is also known that MMPs are important for cancer proliferation, infiltration and metastasis [Protein, Nucleic Acid and Enzyme, 42, 2386 (1997)], and it is reported that MMP inhibitors have carcinostatic activity [SCRIP, 2349, 20 (1998)].

Furthermore, it is suggested that MT4-MMP is expressed in leukocytes and thus may be involved in the migration and infiltration of leukocytes.

From what have been described so far, MMPs may be used for markers for diagnosing arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, wounds, corneal ulcer, tissue injury or inflammations associated with infiltration of leukocytes, and inhibitors of MMPs are useful for preventing or treating these diseases.

The already reported MT4-MMP gene [Cancer Research, 56, 944 (1996)] does not include a transcription initiation site nor has such a domain structure as seen in known membrane-type MMPs such as MT1-MMP. Therefore, this gene represents a sequence encoding a non-physiological peptide not expressed *in vivo*.

The present invention provides a novel, membrane-type matrix metalloproteinase polypeptide [hereinafter, sometimes abbreviated to MT4-MMP(2)] that is, different from the

hitherto reported MT4-MMP, physiologically active; a DNA encoding the metalloproteinase polypeptide; a method of producing the metalloproteinase polypeptide; and a method of screening for inhibitors or activators of the metalloproteinase polypeptide using the polypeptide or the DNA encoding the polypeptide.

The present invention also provides physiologically active, novel, human and mouse membrane-type matrix metalloproteinase polypeptides (hereinafter, abbreviated to human or mouse MT5-MMP); DNAs encoding the metalloproteinase polypeptides; a method of producing the metalloproteinase polypeptides; and a method of screening for inhibitors or activators of the metalloproteinase polypeptides using the polypeptides or the DNAs encoding the polypeptides.

DISCLOSURE OF THE INVENTION

The present inventor has made intensive and extensive researches based on the assumption that the known human MT4-MMP is not a protein having the inherent activity of MT4-MMP and that a true MT4-MMP protein having the activity should exist. Thus, the present invention has been achieved.

Also, the present inventor has made intensive and extensive researches based on the assumption that useful and novel membrane-type MMPs should exist other than hitherto known membrane-type MMPs that are considered useful in pharmaceutical purposes. Thus, the present invention has been achieved.

The present invention relates to the following inventions (1) to (32).

- (1) A polypeptide consisting of the amino acid sequence as shown in SEQ ID NO: 1.
- (2) A polypeptide having an amino acid sequence wherein one or several amino acids are deleted, substituted or added in the amino acid sequence of the polypeptide of (1) above and having metalloproteinase activity.
- (3) A polypeptide consisting of the amino acid sequence as shown in SEQ ID NO: 2.
- (4) A polypeptide having an amino acid sequence wherein one or several amino acids are deleted, substituted or added in the amino acid sequence of the polypeptide of (3) above and having metalloproteinase activity.

The deletion, substitution or addition mentioned in (2) and (4) above can be made by site-specific mutagenesis that was a well-known technique prior to the filing of the present application. "One or several amino acids" means the number of amino acids that can be deleted, substituted or added by site-specific mutagenesis. The polypeptide having an amino acid sequence wherein one or several amino acids are deleted, substituted or added in the amino acid sequence and having metalloproteinase activity can be prepared based on those methods described in Molecular Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor Laboratory Press (1989) (hereinafter, abbreviated to Molecular Cloning 2nd Ed.); Current Protocols in Molecular Biology, Supplement 1-38, John Wiley & Sons (1987-1997) (hereinafter, abbreviated to Current Protocols 1-38); Nucleic Acid Research, 10, 6487 (1982); Proc. Natl. Acad. Sci. USA, 79, 6409 (1982); Gene, 34, 315 (1985), Nucleic Acids Research, 13, 4431 (1985); Proc. Natl. Acad. Sci. USA, 82, 488 (1985); Proc. Natl. Acad. Sci. USA, 81, 5662 (1984); Science, 224, 1431 (1984); PCT WO85/00817 (1985); Nature, 316, 601 (1985) and so forth.

- (5) A polypeptide consisting of the amino acid sequence as shown in SEQ ID NO: 5.
- (6) A polypeptide having an amino acid sequence wherein one or several amino acids are deleted, substituted or added in the amino acid sequence of the polypeptide of (5) above and having metalloproteinase activity.
- (7) A polypeptide consisting of the amino acid sequence as shown in SEQ ID NO: 6.
- (8) A polypeptide having an amino acid sequence wherein one or several amino acids are deleted, substituted or added in the amino acid sequence of the polypeptide of (7) above and having metalloproteinase activity.
- (9) A DNA encoding the polypeptide of any one of (1) to (4) above.
- (10) A DNA encoding the polypeptide of any one of (5) to (8) above.
- (11) A DNA consisting of the nucleotide sequence of positions 86-1846 of SEQ ID NO: 3 or positions 100-1917 of SEQ ID NO: 4, or a DNA which hybridizes to the DNA under stringent conditions and which encodes a polypeptide having metalloproteinase activity.

The above expression "a DNA which hybridizes under stringent conditions" means a DNA that is obtained by colony hybridization, plaque hybridization, Southern blot

hybridization or the like using, as a probe, a DNA consisting of the nucleotide sequence of positions 86-1846 of SEQ ID NO: 3 or positions 100-1917 of SEQ ID NO: 4. Specifically, a DNA which can be identified by carrying out a hybridization at 65°C in the presence of 0.7-1.0 mol/L NaCl using a filter on which the DNA derived from colony or plaque is immobilized, and then washing the filter in 0.1-2 x SSC (saline-sodium citrate) solution (1x SSC solution is composed of 150 mmol/L sodium chloride and 15 mmol/L sodium citrate) at 65°C.

Hybridization may be carried out based on those methods described in laboratory manuals such as Molecular Cloning 2nd Ed., Current Protocol in Molecular Biology, and DNA Cloning 1: Core Techniques, A Practical Approach, Second Edition, Oxford University Press (1995).

Specific examples of hybridizable DNAs include DNAs having at least 80% or more, preferably 95% or more homology to the nucleotide sequence of positions 86-1846 of SEQ ID NO: 3 or positions 100-1917 of SEQ ID NO: 4.

(12) A DNA consisting of the nucleotide sequence of positions 75-1928 of SEQ ID NO: 7 or positions 1-1935 of SEQ ID NO: 8, or a DNA which hybridizes to the DNA under stringent conditions and which encodes a polypeptide having metalloproteinase activity.

The above expression "a DNA which hybridizes under stringent conditions" means a DNA that is obtained by colony hybridization, plaque hybridization, Southern blot hybridization or the like using, as a probe, a DNA consisting of the nucleotide sequence of positions 75-1928 of SEQ ID NO: 7 or positions 1-1935 of SEQ ID NO: 8. Specifically, a DNA which can be identified by carrying out a hybridization at 65°C in the presence of 0.7-1.0 mol/L NaCl using a filter on which the DNA derived from colony or plaque is immobilized, and then washing the filter in 0.1-2 x SSC (saline-sodium citrate) solution (1x SSC solution is composed of 150 mmol/L sodium chloride and 15 mmol/L sodium citrate) at 65°C.

Specific examples of hybridizable DNAs include DNAs having at least 80% or more, preferably 95% or more homology to the nucleotide sequence of positions 75-1928 of SEQ ID NO: 7 or positions 1-1935 of SEQ ID NO: 8.

(13) A recombinant DNA that is obtained by integrating the DNA of any one of (9) to (12) above into a vector.

(14) A transformant comprising the recombinant DNA of (13) above.

(15) The transformant of (14) above, wherein said transformant is a microorganism belonging to the genus *Escherichia*.

(16) The transformant of (15) above, wherein said microorganism belonging to the genus *Escherichia* is *Escherichia coli*.

(17) A method of producing the polypeptide of any one of (1) to (8) above, comprising culturing a transformant comprising a recombinant DNA obtained by integrating a DNA encoding the polypeptide into a vector in a medium, allowing the polypeptide to be produced and accumulated in the culture, and recovering the polypeptide from the culture.

(18) An oligonucleotide selected from an oligonucleotide having a nucleotide sequence identical with a nucleotide sequence consisting of consecutive 5 to 60 bases of the DNA of (9) or (11) above; an oligonucleotide having a nucleotide sequence complementary to the nucleotide sequence of said oligonucleotide; or an oligonucleotide derivative of any one of the above oligonucleotides.

(19) An oligonucleotide selected from an oligonucleotide having a nucleotide sequence identical with a nucleotide sequence consisting of consecutive 5 to 60 bases of the DNA of (10) or (12) above; an oligonucleotide having a nucleotide sequence complementary to the nucleotide sequence of said oligonucleotide; or an oligonucleotide derivative of any one of the above oligonucleotides.

(20) A method of detecting an mRNA encoding the polypeptide of any one of (1) to (8) above using the oligonucleotide of (18) or (19) above.

(21) A method of inhibiting expression of the polypeptide of any one of (1) to (8) using the oligonucleotide of (18) or (19) above.

(22) A method of screening for an inhibitor or an activator of the polypeptide of any one of (1) to (8) above, which comprises using the polypeptide and a cell that expresses the polypeptide.

(23) A diagnostic agent, therapeutic agent or prophylactic agent for arthrosis deformans,

rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, wounds, corneal ulcer, tissue injury or inflammations associated with infiltration of leukocytes, wherein said agent comprises the polypeptide of any one of (1) to (4) above.

(24) A diagnostic agent, therapeutic agent or prophylactic agent for arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, wounds, corneal ulcer, tissue injury, inflammations associated with infiltration of leukocytes, brain disorders at the time of cerebral apoplexy, Alzheimer's disease, dementia, multiple sclerosis, Parkinson's disease or brain tumor, wherein said agent comprises the polypeptide of any one of (5) to (8) above.

(25) A diagnostic agent, therapeutic agent or prophylactic agent for arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, wounds, corneal ulcer, tissue injury or inflammations associated with infiltration of leukocytes, wherein said agent comprises the DNA of (9) or (11) above.

(26) A diagnostic agent, therapeutic agent or prophylactic agent for arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, wounds, corneal ulcer, tissue injury, inflammations associated with infiltration of leukocytes, brain disorders at the time of cerebral apoplexy, Alzheimer's disease, dementia, multiple sclerosis, Parkinson's disease or brain tumor, wherein said agent comprises the DNA of (10) or (12) above.

(27) A diagnostic agent, therapeutic agent or prophylactic agent for arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact

dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, wounds, corneal ulcer, tissue injury or inflammations associated with infiltration of leukocytes, wherein said agent comprises the oligonucleotide of (18) above.

(28) A diagnostic agent, therapeutic agent or prophylactic agent for arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, wounds, corneal ulcer, tissue injury, inflammations associated with infiltration of leukocytes, brain disorders at the time of cerebral apoplexy, Alzheimer's disease, dementia, multiple sclerosis, Parkinson's disease or brain tumor, wherein said agent comprises the oligonucleotide of (19) above.

(29) A vector for gene therapy for treating arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, wounds, corneal ulcer, tissue injury or inflammations associated with infiltration of leukocytes, wherein said vector is obtained by integrating the DNA of (9) or (11) above, or the oligonucleotide of (18) above into a vector.

(30) A vector for gene therapy for treating arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, wounds, corneal ulcer, tissue injury, inflammations associated with infiltration of leukocytes, brain disorders at the time of cerebral apoplexy, Alzheimer's disease, dementia, multiple sclerosis, Parkinson's disease or brain tumor, wherein said vector is obtained by integrating the DNA of (10) or (12) above, or the oligonucleotide of (19) above into a vector.

(31) A method of screening for a compound that regulates the expression of a gene encoding the polypeptide of any one of (1) to (8) above, which comprises contacting a cell that expresses the polypeptide with a test sample.

(32) The method of (31) above, wherein said compound that regulates the expression of a gene is detected by determining the amount of mRNA encoding the polypeptide of any one of (1) to (8) above.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 shows an alignment of the amino acid sequences of human MT5-MMP and mouse MT5-MMP with the amino acid sequences of human MT1-MMP, MT2-MMP, MT3-MMP and MT4-MMP(2).

Mark "*" indicates identical amino acid residues.

Mark "." indicates similar amino acid residues.

(Amino acid residues are represented by one-letter abbreviations.)

In this Figure, "kb" means kilobase pairs.

Fig. 2 shows the results of an experiment in which a mouse MT5-MMP partial peptide (i.e., propeptide domain + active domain; "MT5 Δ C" in this Figure) of various concentrations was reacted with pro-MMP-2 to thereby examine the peptide's ability to cleave and activate pro-MMP-2.

As a positive control, APMA was used. As a result, activation was recognized in an MMP concentration dependent manner. In this Figure, "Active" shows activated MMP-2.

BEST MODES FOR CARRYING OUT THE INVENTION

Hereinbelow, the present invention will be described in detail.

[1] Acquisition of the DNAs encoding the Novel Matrix Metalloproteinase Polypeptides of the Present Invention

(1) Preparation of cDNA Libraries

In order to construct a cDNA library, total RNA or mRNA is prepared from an appropriate cell or tissue.

As a method for preparing total RNA, the guanidine thiocyanate-caesium trifluoroacetate method [Methods in Enzymology, 154, 3 (1987)], the acid guanidine thiocyanate/phenol/chloroform (AGPC) method [Analytical Biochemistry, 162, 156 (1987);

Experimental Medicine, 9, 1937 (1991)]; or the like may be used.

As a method for preparing mRNA (as poly(A)⁺ RNA) from total RNA, a method using oligo(dT) immobilized cellulose column (Molecular Cloning 2nd Ed.), a method using oligo(dT) latex [Cell Engineering, Supplement 8, "New Cell Engineering Experiment Protocols", SHUJUNSHA Co., pp.48-52; Nucleic Acids Res., Symposium Series, 19, 61 (1988)] or the like may be used.

Alternatively, mRNA may be prepared directly from a tissue or cell using a commercial kit such as First Track mRNA Isolation Kit (Invitrogen) or Quick Prep mRNA Purification Kit (Pharmacia).

In the case of MT4-MMP(2), preferably, types of cDNA libraries which contained ESTs of the DNA encoding MT4-MMP found in databases are ascertained, and then cells or tissues that were used for the construction of those libraries, or cell strains or the like derived from those tissues may be used as an appropriate cell or tissue. In the case of MT5-MMP, it is preferable to use tissues such as brain and kidney or cell strains derived from those tissues as an appropriate cell or tissue.

From the resultant total RNA or mRNA, a cDNA library is constructed by conventional methods.

Specific examples of methods for constructing cDNA libraries include those described in Molecular Cloning 2nd Ed.; Current Protocols 1-38; DNA Cloning 1: Core Techniques, A practical Approach, Second Edition, Oxford University Press (1995); etc. or methods using commercial kits such as SuperScript Plasmid System for cDNA Synthesis and Plasmid Cloning manufactured by Gibco BRL and ZAP-cDNA Synthesis Kit manufactured by Stratagene.

As a cloning vector for constructing a cDNA library, any vector, such as a phage vector or plasmid vector, may be used as long as it is capable of autonomous replication in *E. coli* K12 strain.

Specifically, ZAP Express [Stratagene; Strategies, 5, 58 (1992)], pBluescript II SK(+) [Nucleic Acids Research, 17, 9494 (1989)], Lambda ZAP II {Stratagene), λ gt10, λ gt11 [DNA Cloning, A Practical Approach, 1, 49 (1985)], λ TriplEx (Clontech), λ ExCell

(Pharmacia), pT7T318U (Pharmacia), pcD2 [Mol. Cell. Biol., 3, 280 (1983)], pUC18 [Gene, 33, 103 (1985)], pAMo [J. Biol. Chem., 268, 22782-22787 (1993); also called as "pAMoPRC3Sc" (Japanese Unexamined Patent Publication No. 05-336963) or the like may be used.

As a host microorganism, any microorganism may be used as long as it belongs to *Escherichia coli*. Specifically, *Escherichia coli* XL1-Blue MRF' [Stratagene; Strategies 5, 81 (1992)], *Escherichia coli* C600 [Genetics, 39, 440 (1954)], *Escherichia coli* Y1088 [Science, 222, 778 (1983)], *Escherichia coli* Y1090 [Science, 222, 778 (1983)], *Escherichia coli* NM522 [J. Mol. Biol., 166, 1 (1983)], *Escherichia coli* K802 [J. Mol. Biol., 16, 118 (1966)], *Escherichia coli* JM105 [Gene, 38, 275 (1985)], *Escherichia coli* SOLRTM Strain (Stratagene), *Escherichia coli* LE392 (Molecular Cloning 2nd Ed.) or the like may be used.

In addition to cDNA libraries constructed by the above-described methods, commercial cDNA libraries may also be used.

Examples of commercial cDNA libraries include cDNA libraries of individual organs derived from animals such as human, bovine, mouse, rat or rabbit manufactured by Clontech, Lifetech Oriental, etc.

(2) Aquisition of the DNAs of the Invention

cDNA clones containing the DNA of the present invention may be selected from the cDNA library prepared in (1) above by such method as colony hybridization or plaque hybridization (Molecular Cloning 2nd Ed.) using a radioactively or fluorescently labeled probe.

As a probe for MT4-MMP(2) gene, an oligonucleotide based on the nucleotide sequence of a DNA encoding MT4-MMP (a part of which has been elucidated) may be used. For MT5-MMP gene, an oligonucleotide based on the nucleotide sequence of a DNA encoding MT3-MMP may be used.

From the resultant clones of interest, mRNA is obtained as described above and then cDNA is synthesized.

An adaptor is added to both ends of the resultant cDNA. Using a primer based on the

sequence of this adaptor and a gene-specific primer based on the partially known sequence of the gene of interest, 5' RACE (rapid amplification of cDNA ends) and 3' RACE [Proc. Natl. Acad. Sci. USA, 85, 8998 (1988)] are carried out to obtain a cDNA fragment located 5' to the primer sequence and a cDNA fragment located 3' to the primer sequence.

By ligating the resultant cDNA fragments, a full-length cDNA can be obtained.

The nucleotide sequence of the thus obtained DNA fragment can be determined by integrating into a vector the fragment as it is or the fragment digested with an appropriate restriction enzyme by conventional methods and then analyzing the sequence by conventional methods such as the dideoxy method by Sanger et al. [Proc. Natl. Acad. Sci. USA, 74, 5463 (1977)] or with a DNA sequencer manufactured by Perkin Elmer (373A DNA Sequencer), Pharmacia, LI-COR, etc.

In order to determine the nucleotide sequence of the genomic DNA fragment encoding the polypeptide of the present invention, conventional methods for chromosomal DNA cloning (Molecular Cloning 2nd Ed.) can be used.

Briefly, chromosomal DNA from cells expressing the polypeptide of the present invention [such as monocytic THP-1 cells for MT4-MMP(2); such as brain or kidney cells for MT5-MMP] is digested with a restriction enzyme. The digested fragments are cloned into a conventional plasmid vector or phage vector to construct a genomic library.

The genomic library is screened using, as a probe, the DNA fragment obtained and sequenced as described above in the same manner as in the cDNA cloning described above. Thus, clones containing the genomic gene encoding the polypeptide of the present invention can be obtained.

Using the resultant clones, the nucleotide sequence of the genomic gene can be determined by the above-described method.

It is also possible to obtain a DNA of interest derived from other tissues or other animals (e.g. human) by selecting DNAs that hybridize to the DNA obtained by the above-described method under stringent conditions.

Alternatively, a DNA of interest may be chemically synthesized with a DNA synthesizer based on the nucleotide sequence information obtained by the above-described

method. As a DNA synthesizer, one using the thiophosphite method manufactured by Shimadzu Corp., a DNA synthesizer model 392 using the phosphoamidite method manufactured by Perkin Elmer, or the like may be enumerated.

The novelty of the nucleotide sequence obtained can be confirmed by searching DNA sequence databases of GenBank, EMBL, DDBJ, etc. using a homology search program such as BLAST. If the nucleotide sequence is found to be novel, it is converted into an amino acid sequence. Then, amino acid sequence databases of GenPept, PIR, Swiss-Prot, etc. are searched using a homology search program such as FASTA or FrameSearch to thereby search for existing genes having homology to the novel nucleotide sequence.

As a DNA encoding MT4-MMP(2), the polypeptide of the present invention, that has been confirmed to have a novel nucleotide sequence by the above-described method, a DNA having the nucleotide sequence as shown in SEQ ID NO: 3 or SEQ ID NO: 4 may be given, for example.

As a plasmid comprising a DNA having the nucleotide sequence as shown in SEQ ID NO: 3, plasmid pmMT4/pBSSK may be given. As a plasmid comprising a DNA having the nucleotide sequence as shown in SEQ ID NO: 4, plasmid phMT4/pBSIIS may be given.

Escherichia coli pmMT4/pBSSK comprising plasmid pmMT4/pBSSK and *Escherichia coli* phMT4/pBSIIS comprising plasmid phMT4/pBSIIS were deposited as FERM BP-6528 and FERM BP-6530, respectively, on September 25, 1998 with National Institute of Bioscience and Human-Technology, Agency of Industrial Science and Technology located at 1-3, Higashi 1-chome, Tsukuba City, Ibaraki Pref., Japan (postal code: 305-8566).

As a DNA encoding MT5-MMP, another polypeptide of the present invention, that has been confirmed to have a novel nucleotide sequence by the above-described method, a DNA having the nucleotide sequence as shown in SEQ ID NO: 7 or SEQ ID NO: 8 may be given, for example.

As a plasmid comprising a DNA having the nucleotide sequence as shown in SEQ ID NO: 7, plasmid pmMT5/pBSSK may be given. As a plasmid comprising a DNA having the nucleotide sequence as shown in SEQ ID NO: 8, plasmid phMT5/pGEM may be given.

Escherichia coli pmMT5/pBSSK comprising plasmid pmMT5/pBSSK and

Escherichia coli phMT5/pGEM comprising plasmid phMT5/pGEM were deposited as FERM BP-6529 and FERM BP-6531, respectively, on September 25, 1998 with National Institute of Bioscience and Human-Technology, Agency of Industrial Science and Technology located at 1-3, Higashi 1-chome, Tsukuba City, Ibaraki Pref., Japan (postal code: 305-8566).

(3) Preparation of the Oligonucleotides of the Invention

Using the DNAs and DNA fragments of the present invention obtained in the above-described method, oligonucleotides (anti-sense and sense) comprising a partial sequence of the DNAs of the present invention can be prepared by conventional methods or with the DNA synthesizer mentioned above.

Examples of such oligonucleotides include a DNA having the same sequence as that of consecutive 5 to 60 bases within the nucleotide sequences of the above-described DNAs, or a DNA complementary thereto. Specifically, as oligonucleotides comprising a partial sequence of MT4-MMP(2) gene, a DNA having a nucleotide sequence identical with a nucleotide sequence consisting of consecutive 5 to 60 bases in the nucleotide sequence as shown in SEQ ID NO: 3 or 4, or a DNA complementary thereto may be given. As oligonucleotides comprising a partial sequence of MT5-MMP gene, a DNA having a nucleotide sequence identical with a nucleotide sequence consisting of consecutive 5 to 60 bases in the nucleotide sequence as shown in SEQ ID NO: 7 or 8, or a DNA complementary thereto may be given. When oligonucleotides are used as a sense primer and an anti-sense primer, the above-described oligonucleotides are preferably used which are not greatly different between the selected two in melting temperature (T_m) and in the number of bases.

Furthermore, derivatives of these oligonucleotides may also be used as the oligonucleotide of the present invention.

Some of the examples of such oligonucleotide derivatives include oligonucleotide derivatives in which phosphodiester bonds are converted to phosphorothioate bonds; oligonucleotide derivatives in which phosphodiester bonds are converted to N 3'-P5' phosphoamidate bonds; oligonucleotide derivatives in which ribose and phosphodiester bonds are converted to peptide-nucleic acid bonds; oligonucleotide derivatives in which uracil is

substituted by C-5 propynyluracil; oligonucleotide derivatives in which uracil is substituted by C-5 thiazoluracil; oligonucleotide derivatives in which cytosine is substituted by C-5 propynylcytosine; oligonucleotide derivatives in which cytosine is substituted by phenoxazine-modified cytosine; oligonucleotide derivatives in which ribose is substituted by 2'-O-propylribose; or oligonucleotide derivatives in which ribose is substituted by 2'-methoxyethoxyribose [Cell Engineering, 16, 1463 (1997)].

[2] Preparation of the Matrix Metalloproteinase Polypeptides of the Invention

(1) Preparation of Transformants

In order to express in a host cell the DNA of the present invention obtained by the method described in [1] above, methods described in Molecular Cloning 2nd Ed. and Current Protocols 1-38, for example, may be used.

Briefly, a recombinant expression vector is prepared by inserting the DNA of the present invention downstream of a promoter in an appropriate vector. Then, by introducing the recombinant vector into a host cell, a transformant that expresses the polypeptide of the present invention can be obtained.

As a host cell, any cell such as a bacterium, yeast, animal cell, or insect cell may be used as long as it is capable of expressing the gene of interest.

As an expression vector, a vector which is capable of autonomously replicating or integrating into chromosome in the above host cell, and which comprises a promoter at a site appropriate for transcription of the DNA of the present invention, is used.

When a procaryote such as a bacterium is used as the host cell, it is preferred that the expression vector for the polypeptide gene of the present invention be capable of autonomous replication in the procaryote and, at the same time, a recombinant vector composed of a promoter, a ribosome binding sequence, the DNA of the present invention, and a transcription termination sequence. The vector may also contain a gene that controls the promoter.

Examples of expression vectors which may be used in the present invention include pKK233-2 (Pharmacia), pSE280 (Invitrogen), pGEMEX-1 (Promega), pQE-8 (Qiagen), pKYP10 (Japanese Unexamined Patent Publication No. 58-110600), pKYP200 [Agric. Biol.

Chem., 48, 669 (1984)], pLSA1 [Agric. Biol. Chem., 53, 277 (1989)], pGEL1 [Proc. Natl. Acad. Sci. USA, 82, 4306 (1985)], pBluescript II SK(-) (Stratagene), pGEX (Pharmacia), and pET-3 (Novagen).

As a promoter, any promoter may be used as long as it can direct the expression of the gene of interest in a host cell such as *E. coli* or *Bacillus subtilis*. For example, an *E. coli*- or phage-derived promoter such as trp promoter (Ptrp), lac promoter, PL promoter, PR promoter or T7 promoter; SP01 promoter; SP02 promoter; or penP promoter may be used. An artificially designed and altered promoter such as a promoter in which two Ptrp promoters are connected in series (Ptrp x 2), tac promoter, lacT7 promoter, or let 1 promoter may also be used.

As a ribosome binding sequence, it is preferable to use a plasmid in which the distance between Shine-Dalgarno sequence and the initiation codon is appropriately adjusted (e.g., 6-18 bp).

In the recombinant vector of the present invention, it is not necessarily required for the expression of the DNA of the present invention to contain a transcription termination sequence, but it is desirable to locate such a sequence immediately downstream of the structural gene.

As a host cell, a microorganism belonging to the genus *Escherichia*, *Serratia*, *Bacillus*, *Brevibacterium*, *Corynebacterium*, *Microbacterium*, *Pseudomonas* or the like may be used. Specific examples of host cells which may be used in the present invention include *Escherichia coli* XL1-Blue, *Escherichia coli* XL2-Blue, *Escherichia coli* DH1, *Escherichia coli* MC1000, *Escherichia coli* KY3276, *Escherichia coli* W1485, *Escherichia coli* JM109, *Escherichia coli* HB101, *Escherichia coli* No.49, *Escherichia coli* W3110, *Escherichia coli* NY49, *Serratia ficaria*, *Serratia fonticola*, *Serratia liquefaciens*, *Serratia marcescens*, *Bacillus subtilis*, *Bacillus amyloliquefaciens*, *Brevibacterium ammoniagenes*, *Brevibacterium immariophilum* ATCC14068, *Brevibacterium saccharolyticum* ATCC14066, *Corynebacterium glutamicum* ATCC13032, *Corynebacterium glutamicum* ATCC14067, *Corynebacterium glutamicum* ATCC13869, *Corynebacterium acetoacidophilum* ATCC13870, *Microbacterium ammoniaphilum* ATCC15354, and *Pseudomonas* sp. D-0110.

As a method for introducing the recombinant vector, any method of introducing

DNA into the above host cell may be used. For example, the method using calcium ions [Proc. Natl. Acad. Sci., USA, 69, 2110 (1972)], the protoplast method (Japanese Unexamined Patent Publication No. 63-248394), or electroporation [Gene, 17, 107 (1982); Molecular & General Genetics, 168, 111 (1979)] may be used.

When a yeast strain is used as the host cell, an expression vector such as YEp13 (ATCC37115), YEp24 (ATCC37051), YCp50 (ATCC37419), pHS19, or pHS15 may be used.

As a promoter, any promoter that can direct the expression of the gene of interest in yeast may be used. For example, PH05 promoter, PGK promoter, GAP promoter, ADH promoter, gal 1 promoter, gal 10 promoter, heat shock polypeptide promoter, MF α 1 promoter, or CUP 1 promoter may be used.

As a host cell, a yeast strain belonging to the genus *Saccharomyces*, *Schizosaccharomyces*, *Kluyveromyces*, *Trichosporon*, *Schwanniomyces*, *Pichia* or the like may be used. Specific examples of yeast strains that may be used in the present invention include *Saccharomyces cerevisiae*, *Schizosaccharomyces pombe*, *Kluyveromyces lactis*, *Trichosporon pullulans*, *Schwanniomyces alluvius*, and *Pichia pastoris*.

As a method for introducing the recombinant vector, any method of introducing DNA into yeast may be used. For example, electroporation [Methods in Enzymology, 194, 182 (1990)], the spheroplast method [Proc. Natl. Acad. Sci., USA, 81, 4889 (1984)], the lithium acetate method [Journal of Bacteriology, 153, 163 (1983)] or the like may be enumerated.

When an animal cell is used as the host, an expression vector such as pAGE107 (Japanese Unexamined Patent Publication No. 3-22979; Cytotechnology, 3, 133 (1990)), pAS3-3 (Japanese Unexamined Patent Publication No. 2-227075), pCDM8 [Nature, 329, 840 (1987)], pcDNAI/Amp (Invitrogen), pREP4 (Invitrogen), or pAGE103 [Journal of Biochemistry, 101, 1307 (1987)] may be used.

As a promoter, any promoter that can direct the expression of the gene of interest in animal cells may be used. Examples of promoters that may be used in the present invention include the promoter of the IE (immediate early) gene of cytomegalovirus (CMV), the early promoter of SV40, a metallothionein promoter, a retrovirus promoter, a heat shock

promoter and SR α promoter. Alternatively, the enhancer of the IE gene of human CMV may be used in combination with the promoter thereof.

Examples of animal cells that may be used in the present invention include human cells such as Namalwa cells, HEK293 cells (ATCC: CRL-1573); simian cells such as COS cells; and Chinese hamster cells such as CHO cells, HBT5637 (Japanese Unexamined Patent Publication No. 63-299).

As a method for introducing the recombinant vector, any method of introducing DNA into animal cells may be used. For example, electroporation [Cytotechnology, 3, 133 (1990)], the calcium phosphate method (Japanese Unexamined Patent Publication No. 2-227075), or lipofection [Proc. Natl. Acad. Sci. USA, 84, 7413 (1987); Virology, 52, 456 (1973)] may be used.

When an insect cell is used as the host, it is possible to express the polypeptide of the present invention according to methods described in, for example, Baculovirus Expression Vectors, A Laboratory Manual, W.H. Freeman and Company, New York (1992); Current Protocols 1-38; and Bio Technology, 6, 47 (1988).

Briefly, a recombinant gene transfer vector and Baculovirus are co-introduced into an insect cell to thereby obtain a recombinant virus in the supernatant of the insect cell culture. Then, the insect cell is infected with the recombinant virus further to allow the production of the polypeptide of the present invention.

As a gene transfer vector that may be used in the above method, pVL1392, pVL1393, pBlueBacIII (all of which are manufactured by Invitrogen) may be enumerated, for example.

As a Baculovirus that may be used in the above method, Autographa californica nuclear polyhedrosis virus that infects insects belonging to the subfamily Hadeniaae may be given, for example.

As an insect cell that may be used in the above method, *Spodoptera frugiperda* ovary cells Sf9 and Sf21 [Baculovirus Expression Vectors, A Laboratory Manual (1992)]; a *Trichoplusia ni* ovary cell High5 (Invitrogen); or the like may be enumerated.

As a method of co-introducing a gene transfer vector and Baculovirus into an insect cell

for preparing a recombinant virus, the calcium phosphate method (Japanese Unexamined Patent Publication No. 2-227075) or lipofection [Proc. Natl. Acad. Sci. USA, 84, 7413 (1987)] may be enumerated, for example.

As a method of expressing the gene, in addition to direct expression, such as secretion production or fusion protein expression may be carried out based on the methods described in Molecular Cloning 2nd Ed.

When the polypeptide of the present invention is expressed by a yeast strain, animal cell or insect cell, a polypeptide to which sugars or sugar chains have been attached can be obtained.

The polypeptide of the present invention can be prepared by culturing the transformant obtained as described above in a medium, allowing the polypeptide of the present invention to be produced and accumulated in the culture, and recovering the polypeptide from the culture.

It is also possible to express the polypeptide of the present invention in a patient *in vivo* by introducing an appropriate expression vector that directs expression of the polypeptide of the present invention into cells taken from the patient's living body and then returning the cells into the body.

(2) Culturing of Transformants

The culturing of the transformant of the present invention in a medium is carried out by conventional methods used for culturing hosts.

As a medium to culture the transformant obtained from a procaryotic host such as *E. coli* or an eucaryotic host such as yeast, either a natural or synthetic medium may be used as long as it contains carbon sources, nitrogen sources and inorganic salts assimilable by the microorganism and is suitable for efficient culturing of the transformant.

As carbon sources, any carbon source may be used as long as it is assimilable by the microorganism. For example, carbohydrates such as glucose, fructose, sucrose, or molasses, starch or starch hydrolysate containing them; organic acids such as acetic acid, propionic acid; and alcohols such as ethanol and propanol may be used.

As nitrogen sources, ammonia; ammonium salts of inorganic or organic acids such as

ammonium chloride, ammonium sulfate, ammonium acetate, ammonium phosphate; other nitrogen-containing compounds; Peptone; meat extract; yeast extract; corn steep liquor; casein hydrolysate; soybean meal and soybean meal hydrolysate; various fermented microorganism cells and digested products thereof; and the like may be used.

As inorganic substances, potassium dihydrogen phosphate, dipotassium hydrogen phosphate, magnesium phosphate, magnesium sulfate, sodium chloride, iron(II) sulfate, manganese sulfate, copper sulfate, calcium carbonate and the like may be used.

Usually, culturing is carried out under aerobic conditions, by such as shaking culture or submerged aeration agitation culture. The culturing temperature is preferably between 15 to 40°C, and the culturing period is usually 16 to 96 hrs. During the culturing, the pH is maintained at 3.0 to 9.0. The pH adjustment is carried out using an inorganic or organic salt, an alkali solution, urea, calcium carbonate, ammonia or the like.

During the culturing, an antibiotic such as ampicillin or tetracycline may be added to the medium if necessary.

When a microorganism transformed with an expression vector using an inducible promoter is cultured, an inducer may be added to the medium if necessary. For example, when a microorganism transformed with an expression vector using Lac promoter is cultured, isopropyl- β -D-thiogalactopyranoside or the like may be added. When a microorganism transformed with an expression vector using trp promoter is cultured, indoleacrylic acid or the like may be added.

As a medium to culture a transformant obtained from an animal cell as a host, commonly used RPMI1640 medium [The Journal of the American Medical Association, 199, 519 (1967)], Eagle's MEM medium [Science, 122, 501 (1952)], DMEM medium [Virology, 8, 396 (1959)], 199 medium [Proceeding of the Society for the Biological Medicine, 73, 1 (1950)] or one of these media supplemented with fetal bovine serum, etc. may be used.

Usually, the culturing is carried out at pH 6-8, at 30-40°C in the presence of 5% CO₂ for 1 to 7 days.

During the culturing, an antibiotic such as kanamycin, penicillin, or streptomycin may be added to the medium if necessary.

As a medium to culture a transformant obtained from an insect cell as a host, commonly used TNM-FH medium (Pharmingen), Sf-900 II SFM medium (Life Technologies), ExCell400 or ExCell405 (both from JRH Biosciences), Grace's Insect Medium [Nature, 195, 788 (1962)] or the like may be used.

Usually, culturing is carried out at pH 6-7 at 25-30°C for 1 to 5 days.

During the culturing, an antibiotic such as gentamycin may be added to the medium if necessary.

(3) Isolation and Purification of the Expressed Polypeptides

Conventional methods of enzyme isolation/purification may be used to isolate and purify the polypeptides expressed by the method described above from the culture of the above-described transformant. For example, when the polypeptide of the present invention is expressed in a dissolved state in cells, the cells are harvested by centrifugation after completion of the culturing, and then suspended in an aqueous buffer. Subsequently, the cells are disrupted with a sonicator, French press, Manton-Gaulin homogenizer, Dynomill or the like to thereby obtain a cell-free extract, which is then centrifuged to obtain a supernatant. From this supernatant, a purified sample may be obtained by conventional enzyme isolation/purification methods. For example, the solvent extraction method; salting out with ammonium sulfate or the like; desalting; precipitation with organic solvents; anion exchange chromatography using resins such as Q-Sepharose, diethylaminoethyl (DEAE)-Sepharose, DIAION HPA-75 (Mitsubishi Chemical Corp.); cation exchange chromatography using resins such as S-Sepharose FF (Pharmacia); hydrophobic chromatography using resins such as butyl Sepharose, phenyl Sepharose; gel filtration using molecular sieve; affinity chromatography; and electrophoresis such as chromatofocusing, isoelectric focusing; may be used independently or in combination.

When the polypeptide of the present invention is expressed in an insoluble form within cells, the cells are harvested and disrupted in the same manner as described above. Then, the cells are centrifuged to obtain the precipitate fraction, from which the polypeptide is recovered by conventional methods. Subsequently, the polypeptide in an insoluble form is solubilized

with a protein-denaturing agent. The resultant solubilized solution is diluted until the solution no longer contains the denaturing agent or the concentration of the denaturing agent becomes so low that no protein denaturation would occur; or the solubilized solution is dialyzed. Thus, the normal steric structure of the polypeptide is restored. Subsequently, a purified sample can be obtained by using the isolation/purification methods described above.

When the polypeptide of the present invention or a derivative thereof (such as sugar-modified polypeptide) is secreted out of cells, the polypeptide or the derivative can be recovered from the culture supernatant. Briefly, the culture is treated by centrifugation, etc. in the same manner as described above to obtain the soluble fraction. From this soluble fraction, a purified sample can be obtained by using the isolation/purification methods described above. When the polypeptide of the present invention or a derivative thereof (such as sugar-modified polypeptide) is expressed on cell surfaces, the membrane fraction of the cultured cells is dissolved with a surfactant to obtain the soluble fraction. From this soluble fraction, a purified sample can be obtained by using the isolation/purification methods described above.

Alternatively, the polypeptide of the present invention may be prepared by chemical synthesis methods such as the Fmoc (fluorenylmethyloxycarbonyl) method and the tBoc (t-butyloxycarbonyl) method. The polypeptide of the present invention may also be chemically synthesized with peptide synthesizers manufactured by Advanced ChemTech, Perkin Elmer, Pharmacia, Protein Technology Instrument, Synthecell-Vega, PerSeptive, Shimadzu Corp. and so forth.

[3] Detection of the Biological Activity of the Polypeptides of the Invention

The proteinase activity of the polypeptides of the present invention obtained by the method described in [2] above is determined by subjecting a peptide or protein degraded by the polypeptides of the present invention electrophoresis or column chromatography. Alternatively, the activity is determined by measuring degradation of a fluorescence- or isotope-labeled peptide or protein by the polypeptide of the present invention. It is also possible to detect the activity by measuring the state of activation of an enzyme that is

activated by excision of a peptide. The activity may also be measured by using a gel containing a peptide that is degraded by the enzyme in the same manner as in gelatin zymography.

[4] Search for and Identification of Inhibitors or Activators of the Polypeptides of the Invention

A test sample is added to those cells expressing the polypeptide of the present invention prepared by the method described in [2] above, or the polypeptide of the present invention purified by the method described in [2] above from recombinant *E. coli* cells expressing the polypeptide of the present invention prepared by the method described in [2] above.

Then, by comparing the proteinase activity of the polypeptide of the present invention in the presence of the test sample with the activity in the absence of the test sample, it is possible to screen for a substance that enhances the proteinase activity (activator) or a substance that inhibits the proteinase activity (inhibitor).

Specific examples of test samples include synthetic compounds, naturally occurring proteins, artificially synthesized proteins, peptides, saccharides, lipids, modified products or derivatives of these substances; urine, body fluids, tissue extracts, cell culture supernatants and cell extracts from mammals (such as mouse, rat, guinea pig, hamster, pig, sheep, bovine, equine, canine, feline, simian, or human); non-peptidic compounds; fermentation products; and extracts from plants and other organisms.

When a peptide is used as a test sample, a random peptide library may be utilized. Examples of random peptide libraries that may be used in the present invention include peptides on phage [Proc. Natl. Acad. Sci. USA, 87, 6378 (1990); PCT Patent Application Number 96/40189] and peptides on plasmids [United States Patent No. 5,270,170; United States Patent No. 5,338,665].

Peptides that bind to MT4-MMP(2) of the present invention can be obtained by screening a random peptide library. Examples of random peptide libraries that may be used in the present invention include peptides on phage [Proc. Natl. Acad. Sci. USA, 87, 6378 (1990); PCT Patent Application Number 96/40189] and peptides on plasmids [United States

[5] Uses of the DNAs and Polypeptides of the Invention

(1) The DNA of the present invention may be used as a probe in Northern hybridization on RNA that is extracted from human tissues or human-derived cells in the same manner as described in (2) of Section [1] above, to thereby detect or quantitatively determine the mRNA of the polypeptide gene of the present invention in the tissues or cells. By comparing the amounts of RNA expressed in various tissues, the tissue distribution of the polypeptide of the present invention can be elucidated.

Alternatively, the oligonucleotide of the present invention may be used as a primer specific to the DNA of the present invention in RT-PCR [reverse transcription PCR; PCR protocols (1990)] on RNA that is extracted from human tissues or human-derived cells in the same manner as described in (2) of Section [1] above, to thereby detect or quantitatively determine the mRNA of the polypeptide gene of the present invention. These methods of quantitative determination of the mRNA of the polypeptide gene may be used in the diagnosis of disease states in which the gene is involved.

By quantification of the mRNA encoding the polypeptide in various disease model animals, it is possible to reveal the importance of the gene product in diseases. Furthermore, it is possible to evaluate a drug by comparing the amount of expression of the mRNA encoding the polypeptide in the presence or absence of the drug.

(2) The DNA of the present invention or an oligonucleotide having a nucleotide sequence identical with or complementary to a partial nucleotide sequence of the DNA may be used as a probe to carry out *in situ* hybridization [Methods in Enzymology, 254, 419 (1995)] on human tissue section. As a result, more detailed information on the distribution of the polypeptide of the present invention can be obtained, e.g. cells expressing the polypeptide in a given tissue can be specified.

Information as to in which tissue or cell the polypeptide of the present invention is expressed, and information as to what stimulation given to cells changes the amount of expression of the polypeptide obtained by the above-described methods will be useful in

elucidating the physiological functions of the polypeptide of the present invention and its involvement in diseases.

(3) The DNA of the present invention may be used as a probe to carry out Southern hybridization (Molecular Cloning 2nd Ed.) on genomic DNA. As a result, mutations in the gene encoding the polypeptide of the present invention can be detected. By detecting such mutations, it is possible to diagnose those diseases which may be caused by mutations of the gene. Specifically, with respect to MT4-MMP(2), diseases such as arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, and inflammations associated with infiltration of leukocytes may be diagnosed. With respect to MT5-MMP, diseases such as arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, brain disorders at the time of cerebral apoplexy, Alzheimer's disease, dementia, multiple sclerosis, Parkinson's disease, brain tumor, and inflammations associated with infiltration of leukocytes may be diagnosed.

(4) The anti-sense oligonucleotides (RNA/DNA) of the present invention are expected to be applicable to treatment or prevention of diseases in which the gene encoding the polypeptide of the present invention may be involved in their onset, by inhibiting the transcription of the gene or the translation of the mRNA [Chemistry 46, 681 (1991); Bio Technology, 9, 358 (1992)]. With respect to MT4-MMP(2), specific examples of such diseases include arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, and inflammations associated with infiltration of leukocytes. With respect to MT5-MMP, specific examples of such diseases include arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor,

brain disorders at the time of cerebral apoplexy, Alzheimer's disease, dementia, multiple sclerosis, Parkinson's disease, brain tumor, and inflammations associated with infiltration of leukocytes.

The above-described anti-sense oligonucleotide is designed and prepared based on a partial nucleotide sequence of the DNA encoding the polypeptide of the present invention, preferably a nucleotide sequence complementary to 10-50 bases within the translation initiation region, and then administered into the living bodies of subjects.

Pharmaceuticals containing the DNA of the present invention are prepared or administered in the same manner as described below except that the DNA of the present invention is used instead of the polypeptide of the present invention.

(5) The polypeptide of the present invention can be obtained by using the DNA of the present invention in accordance with the method described in [2] above. With respect to MT4-MMP(2), a polypeptide of the present invention is used for a diagnostic agent, therapeutic agent or prophylactic agent for diseases such as arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, and inflammations associated with infiltration of leukocytes. With respect to MT5-MMP, a polypeptide of the present invention is used for a diagnostic agent, therapeutic agent or prophylactic agent for diseases such as arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, brain disorders at the time of cerebral apoplexy, Alzheimer's disease, dementia, multiple sclerosis, Parkinson's disease, brain tumor, and inflammations associated with infiltration of leukocytes is contemplated.

Although it is possible to administer the polypeptide of the present invention alone as a diagnostic agent or therapeutic agent, usually it is preferred that the polypeptide of the present invention be administered as a pharmaceutical preparation obtained by mixing the polypeptide with one or more pharmacologically acceptable carriers and formulating by any of the well-known methods in the technical field of pharmaceuticals. Preferably, a sterile solution of the

polypeptide dissolved in water or an aqueous carrier such as an aqueous solution of NaCl, glycine, glucose or human albumin is used. Pharmacologically acceptable additives such as buffers and isotonic agents that bring liquid preparations close to physiological conditions may also be added. For example, sodium acetate, sodium chloride, sodium lactate, potassium chloride, or sodium citrate may be added. The pharmaceutical preparation may be freeze-dried for storage and dissolved in an appropriate solvent at the time of use.

It is desirable to select the best route of administration that would be most effective for the treatment intended. Usually, parenteral routes such as subcutaneous, intramuscular, intravenous, or intratracheal route are used.

(6) The DNAs of the present invention (sense DNAs and anti-sense DNAs) or oligonucleotides comprising a part of the nucleotide sequences thereof may be incorporated as a single-stranded or double-stranded DNA or oligonucleotide into viral vectors such as retrovirus, adenovirus, adeno-associated virus or other vectors to prepare vectors for gene therapy, and may be used in such therapy.

EXAMPLES

Hereinbelow, the present invention will be described more specifically with reference to the following Examples. However, the scope of the present invention is not limited by these Examples.

EXAMPLE 1. Cloning of the Gene of Mouse MT4-MMP-Related Protein [MT4-MMP(2)]

Since MT4-MMP gene is highly expressed in the human brain, a brain cDNA library from mouse 17-day embryo was prepared using ZAP-cDNA Synthesis Kit (Stratagene) according to the manual attached to the Kit.

Using a partial sequence of the human MT4-MMP gene (positions 233-1899 of SEQ ID NO: 17) as a probe, the resultant cDNA library was screened by plaque hybridization.

Several of the positive clones that hybridized to the above probe were analyzed for their nucleotide sequences. All of the analyzed clones contained a signal peptide sequence that is considered missing in the reported human MT4-MMP gene; the longest clone was 3.5 kb.

Therefore, it was considered that an mRNA corresponding to the DNA of SEQ ID NO: 3 which can express the 587 amino acid MT4-MMP(2) shown in SEQ ID NO: 1 is expressed in mouse.

EXAMPLE 2. Cloning of Human MT4-MMP (2) Gene

EST clones relating to the human MT4-MMP gene were searched for through databases. However, no clones were registered which contain a sequence encoding a signal peptide as seen in the above-mentioned mouse gene. Therefore, it was considered that secretion-type human MT4-MMP gene does not exist or there are reasons that make the isolation thereof difficult.

A human brain cDNA library (Clontech) was screened using a partial sequence of the mouse MT4-MMP(2) gene, as a probe, from Example 1 encoding an N-terminal region representing the signal peptide. However, the gene of interest could not be isolated. Then, the inventors analyzed 5' regions of transcripts by 5' RACE. For this analysis, monocyte-derived THP-1 (ATCC TIB-202; American Type Culture Collection) cells were used in which expression of MT4-MMP mRNA had been confirmed.

Briefly, a cDNA was prepared using poly(A)⁺ RNA isolated from human THP-1 cells, a human MT4-MMP selective primer (SEQ ID NO: 9) and Superscript II (Gibco BRL). A single-stranded oligonucleotide adaptor (SEQ ID NO: 10) was ligated to the resultant cDNA with T4 RNA ligase. Then, a PCR was performed in GC buffer using the MT4-MMP selective primer (SEQ ID NO: 9), an adaptor selective primer (SEQ ID NO: 11) and LA Taq (Takara). After completion of this reaction, another PCR was performed using a gene-selective, other primer (SEQ ID NO: 12) and an adaptor selective primer (SEQ ID NO: 13).

The analysis of the 50 clones revealed that, while 3 clones were cDNA fragments containing an MT4-MMP sequence, 47 clones were cDNA fragments encoding a signal peptide sequence similar to that in mouse MT4-MMP(2). From this, in addition to the downstream region of the propeptide sequence already known, the entire region of the mRNA of SEQ ID NO: 4 encoding human MT4-MMP(2) as shown in SEQ ID NO: 2 containing a signal peptide has been elucidated. Although the nucleotide sequence of an EST clone

H97792 was almost identical with the sequence of the MT4-MMP gene reported by Puente [Cancer Research, 56, 944 (1996); SEQ ID NO: 17], a partial sequence of the catalytic domain was different. The EST clone H97792 was more highly conserved with mouse MT4-MMP(2) gene. When the entire sequence of human MT4-MMP(2) gene was determined newly, differences were found even in the previously sequenced region of the MT4-MMP gene reported by Puente.

Mouse and human MT4-MMP(2) genes are mutually conserved well; their propeptide domains, catalytic domains, hinge domains and hemopexin-like domains had 87%, 87%, 78% and 96% homology, respectively. Their signal peptide domains and transmembrane domains had relatively low similarities of 54% and 35%, respectively. When the catalytic domain of human MT4-MMP(2) gene were compared with the catalytic domains of MT1-MMP, MT2-MMP and MT3-MMP, the similarities were 36%, 39% and 31%, respectively. These results also supported that mouse MT4-MMP(2) gene is most close to human MT4-MMP(2) gene. Thus, it was concluded that mouse MT4-MMP(2) gene is a mouse homologue to human MT4-MMP(2) gene.

EXAMPLE 3. Expression of MT4-MMP(2) and Detection of the Gene Product

In order to confirm that a gene product is certainly translated from the isolated cDNA, the cDNA was integrated into pSG5 vector (Stratagene) containing an SV 40 promoter. For detecting the expressed product, a FLAG sequence (Eastman Chemical) was integrated downstream of the latent enzyme processing site to thereby enable detection with anti-FLAG antibodies.

COS-1 cells were transfected with mouse or human MT4-MMP(2) expression plasmids. After 48 hr, cells were harvested and lysed followed by detection of FLAG-labeled MT4-MMP by Western blotting. With the use of an anti-FLAG antibody M2 (Eastman Chemical), a specific 66 kDa band in both cells transfected with the expression plasmids was detected.

EXAMPLE 4. Detection and Analysis of MT4-MMP Transcript

Since MT4-MMP transcript has an *Alu* sequence at 5' end, there was a possibility that it

contains intron(s). Using a partial sequence of human MT4-MMP(2) (positions 212-519 of SEQ ID NO: 4) as a probe, hybridized clones were isolated from a library of Health Science Research Resources Bank (Deposit No. LI020) by hybridization, and plasmids were extracted from the resultant clones by conventional methods. Then, the present inventors examined nucleotide sequences around the 5' end region (positions 140-272 of SEQ ID: 17) of MT4-MMP contained in these plasmids.

When MT4-MMP gene was compared with MT4-MMP(2) gene, MT4-MMP nucleotide sequence of the region in which homology no longer exists (positions 1-139 of SEQ ID NO: 17) was almost identical with positions 3008-3147 of the genomic sequence (SEQ ID NO: 18); and a splice donor sequence was found on the border between the region with homology and the region without homology. The sequence encoding the exons of MT4-MMP (positions 140-340 of SEQ ID NO: 17) were almost identical with positions 3148-3280 and positions 3564-3633 of the genomic sequence (SEQ ID NO: 18). From these results, it was concluded that the transcript still containing the first intron is MT4-MMP transcript.

From these results, it was considered that two mRNAs encoding MT4-MMP and MT4-MMP(2) are expressed in human.

In order to discriminate these two transcripts by performing RT-PCR separately, 5' primers specific to individual transcripts (MT4-MMP: SEQ ID NO: 14; MT4-MMP(2): SEQ ID NO: 15) and a common 3' primer (SEQ ID NO: 16) were prepared.

The expression of these transcripts in various cancer cells is shown in Table 1 below.

Table 1. Expression of MT4-MMP(2) and MT4-MMP Transcripts in Cancer Cells

Cancer Cell Line	MT4-MMP(2)	MT4-MMP	Accession Number
Jurkat (T cell)	++	+/-	ATCC TIB-152
Raji (B cell)	-	-	ATCC CCL-86
BJAB (B cell)	-	-	ATCC HB-136
THP-1 (monocytic)	++	+	ATCC TIB-202
K562 (monocytic)	++	-	ATCC CCL-243
U-937 (monocytic)	++	-	ATCC CRL-1593.2
U-251 MG (astrocytoma)	++	-	Hakkoken IFO50288
SK-N-SH (neuroblastoma)	++	-	ATCC HTB-11
no.10 (glioma)	+/-	-	Hakkoken IFO50368
KALS-1 (glioma)	++	-	Hakkoken IFO50434
MKN-7 (gastric)	+	-	Riken RCB0999
MKN-28 (gastric)	-	-	Riken RCB1000
NUGC-4 (gastric)	+	-	HS Found JCRB0834
PANC-1 (pancreatic)	++	+	ATCC CRL-1469
MIA PaCa-2 (pancreatic)	++	+/-	ATCC CRL-1420
SK-HEP-1 (hepatoma)	++	+	ATCC HTB-52
Hep 3B (hepatoma)	++	+	ATCC HB-8064
ZR-75-1 (breast)	++	+	ATCC CRL-1500
MCF7(adenocarcinoma)	++	+	ATCC HTB-22
T-24 (bladder)	++	+	ATCC HTB-4
A375 (melanoma)	++	+	ATCC CRL-1619
HT-1080 (fibrosarcoma)	+	-	ATCC CCL-121

++: strong expression; +: medium expression; +/-: slight expression; -: no expression

ATCC: American Type Culture Collection

HS Found.: Japan Health Sciences Foundation

Riken: The Institute of Physical and Chemical Research

Hakkoken: Institute for Fermentation, Osaka

MT4-MMP was only expressed in those cells where expression of MT4-MMP(2) was recognized.

From these results, it is believed that MT4-MMP(2) is the major transcript and that expression of MT4-MMP also occurs depending on cells under similar transcriptional control.

EXAMPLE 5. Expression of MT4-MMP(2) in mouse Tissues

Tissues of 4-week old mice were excised by organ. RNA was extracted therefrom and used to examine the expression pattern of MT4-MMP(2). Briefly, 20 μ g of total RNA was electrophoresed on 1% agarose gel and transferred onto a nylon membrane followed by Northern blot analysis using 32 P-labeled mouse MT4-MMP(2) gene as a probe, to thereby examine the expression pattern of MT4-MMP(2).

Organs in which particularly high expression was observed were the cerebrum, cerebellum, brainstem, large intestine, uterus, and testis. Little expression was observed in the adrenal, mammary gland, and placenta. The results of expression in mouse were consistent with the results of MT4-MMP expression in human tissues reported by Puente et al. [Cancer Research, 56, 944 (1996)].

In mouse, the expression of MT4-MMP(2) was very high in the brain, and its expression was also observed in some limited organs such as the large intestine, uterus and testis. This presents a contrast to the expression of MT1-MMP and MT2-MMP seen in a relatively wide range of tissues. From this, it is believed that MT4-MMP(2) is involved in the maintenance of homeostasis in tissues through the degradation of extracellular substrates specific to those organs expressing MT4-MMP(2).

EXAMPLE 6. Expression of a Mouse MT4-MMP(2) Partial Peptide (Hemopexin-like Domain) in *E. coli*

A cDNA encoding a mouse MT4-MMP(2) partial peptide (hemopexin-like domain) having an amino acid sequence represented by positions 321-550 of SEQ ID NO: 1 to which a

methionine residue was added at the N-terminus was amplified by polymerase chain reaction (PCR) using the cDNA of mouse MT4-MMP(2) as a template.

The amplified fragment was subcloned into an *E. coli* expression vector pET3a (Takara) and then introduced into *E. coli* BL21 (DE3) pLysS (Takara). This *E. coli* was grown in 1 liter of expression medium in the presence of 100 μ g/ml of ampicillin until OD₆₀₀ reached 0.5. Then, the cells were stimulated with 0.4 mmol/L of isopropyl- β -D-thiogalactopyranoside (IPTG) and cultured for another three hours.

After the culturing, granules (inclusion bodies) consisting of the mouse MT4-MMP(2) partial peptide formed in *E. coli* cells were collected by conventional methods and dissolved in a solubilization solution containing 8 mol/L urea, 50 mmol/L Tris-HCl (pH 8.6) and 20 mmol/L dithiothreitol (DTT). The resultant solution was applied to High Q anion exchange column followed by recovery of the fraction eluted with 0.2 mol/L sodium chloride.

This fraction was diluted with a solution containing 50 mmol/L Tris-HCl (pH 8.6), 6 mol/L urea, 1 mmol/L dithiothreitol, 0.15 mol/L sodium chloride, 5 mmol/L calcium chloride, 100 mmol/L zinc chloride and 0.02% sodium azide. Then, cystamine (final concentration: 20 mmol/L) was added to the resultant dilution. Subsequently, the resultant solution was dialyzed against a solution containing 50 mmol/L Tris-HCl (pH 8.6), 0.15 mol/L sodium chloride, 5 mmol/L calcium chloride, 100 mmol/L zinc chloride, 5 mmol/L β mercaptoethanol, 1 mmol/L 2-hydroxyethyl disulfide and 0.02% sodium azide at 4 °C. Further, dialysis was performed against 10 volumes of a solution containing 50 mmol/L Tris-HCl (pH 7.5), 0.15 mol/L sodium chloride, 5 mmol/L calcium chloride, 50 mmol/L zinc chloride and 0.02% sodium azide (4 hr x 3 times). The dialyzed solution was centrifuged at 22,000xg at 4 °C for 10 min to remove the precipitate.

The supernatant was applied to S-200 column pre-equilibrated with a buffer containing 50 mmol/L Tris-HCl (pH 7.5), 150 mmol/L sodium chloride, 10 mmol/L calcium chloride and 0.02% sodium azide for gel filtration to obtain a mouse MT4-MMP(2) partial peptide corresponding to the hemopexin-like domain.

EXAMPLE 7. Expression of a Human MT4-MMP(2) Partial Peptide (Propeptide Domain +

Active Domain) in *E. coli*

A cDNA encoding a human MT4-MMP(2) partial peptide having an amino acid sequence represented by positions 58-298 of SEQ ID NO: 2 was amplified by polymerase chain reaction (PCR) using the cDNA of human MT4-MMP(2) as a template.

The amplified fragment was subcloned into an *E. coli* expression vector pRSET (Invitrogen). The enzyme was expressed as a fusion protein fused to the 6x His sequence present in the pRSET-derived leader sequence. This vector was introduced into *E. coli* BL21 (DE3) pLysS (Takara). This *E. coli* was grown in 1 liter of expression medium (tryptone, 12 g/L; yeast extract, 24 g/L; sodium chloride, 10 g/L; Tris base, 250 mg/L; glycerol, 4 ml/L) in the presence of 100 μ g/ml ampicillin until OD₆₀₀ reached 0.5. Then, the cells were stimulated with 0.4 mmol/L isopropyl- β -D-thiogalactopyranoside (IPTG) and cultured for another three hours.

After the culturing, granules (inclusion bodies) consisting of the human MT4-MMP(2) partial peptide (propeptide domain + active domain) formed in *E. coli* cells were collected by conventional methods and dissolved in a solubilization solution containing 8 mol/L urea and 50 mmol/L Tris-HCl (pH 8.6). The resultant solution was applied to a nickel chelate column followed by recovery of the fraction eluted with 250 mmol/L imidazole.

This fraction was diluted with a solution containing 50 mmol/L Tris-HCl (pH 8.6), 6 mol/L urea, 20 mmol/L dithiothreitol, 0.15 mol/L sodium chloride, 100 mmol/L calcium chloride, 100 μ mol/L zinc chloride and 0.02% sodium azide (200-fold dilution). Then, cystamine (final concentration: 20 mmol/L) was added to the resultant dilution. Subsequently, the resultant solution was dialyzed against a solution containing 50 mmol/L Tris-HCl (pH 8.6), 0.15 mol/L sodium chloride, 10 mmol/L calcium chloride, 100 μ mol/L zinc chloride, 5 mmol/L β mercaptoethanol, 1 mmol/L 2-hydroxyethyl disulfide and 0.02% sodium azide at 4°C. Further, dialysis was performed against 10 volumes of a solution containing 50 mmol/L Tris-HCl (pH 7.5), 0.15 mol/L sodium chloride, 10 mmol/L calcium chloride, 50 μ mol/L zinc chloride and 0.02% sodium azide (4 hr x 3 times). The thus dialyzed solution was centrifuged at 22,000xg at 4°C for 10 min to remove the precipitate.

The supernatant obtained was concentrated 5-fold with Amicon YM-10 (Millipore) to

prepare a crude enzyme.

EXAMPLE 8. Measurement of the Activity of the Human MT4-MMP(2) Partial Peptide (Active Domain)

a) Activation of the Human MT4-MMP(2) Partial Peptide (Propeptide Domain + Active Domain)

It is known that MMPs are activated by trypsin treatment and then exhibit metalloproteinase activity. Whether MT4-MMP(2) is also activated by such treatment or not was examined by the method described below.

Briefly, trypsin (Wako Purechemical Industries, Ltd.) was added to 200 μ l of the crude MT4-MMP(2) partial peptide (propeptide domain + active domain) solution to give a concentration of 0.1 μ g/ml, and reacted at 37°C for 30 min. Then, phenylmethanesulfonyl fluoride (PMSF) (a serine protease inhibitor) was added to the reaction solution at 1 mmol/L to inactivate the trypsin.

b) Assay

To 10 μ l of the activated enzyme, a measurement buffer or an inhibitor diluted with a measurement buffer (TIMP-1 or TIMP-2; final concentration: 1 μ g/ml) was added to make a 50 μ l solution. To this solution, 50 μ l of 10 μ mol/L fluorescent substrate was added and reacted at 37°C for 120 min. After the completion of each reaction, fluorescence generated by the enzyme reaction was measured. Measurement was carried out under the following conditions: excitation wave length: 320 nm; fluorescence wave length: 395 nm.

The reagents and substrates used in this assay were as described below.

Fluorescent substrate: DMSO stock (10 mmol/L); MOCac-Pro-Leu-Gly-Leu-
A₂pr(Dnp)-Ala-Arg-NH₂ (Peptide Institute, Inc.)

Standard fluorescent substrate: DMSO stock (1 mmol/L); MOCac-Pro-Leu-Gly
(Peptide Institute, Inc.)

Activity measurement buffer: 0.1 mol/L Tris-HCl (pH 7.5; Nacalai Tesque), 0.1 mol/L NaCl
(Nacalai Tesque), 0.01 mol/L CaCl₂ (Wako Purechemical),
0.05% Brij-35 (w/v; Wako Purechemical)

The results of the measurement are shown in Table 2. Similar to other MMPs, the MT4-MMP(2) partial peptide, in particular, the partial peptide after the activation by trypsin exhibited a strong substrate-degrading activity.

It is reported that MT-MMPs are not inhibited by the metalloproteinase inhibitor TIMP-1, but inhibited by TIMP-2 [FEBS Letters, 393, 101 (1996)].

Whether MT4-MMP(2) also has such a nature or not was examined.

As shown in Table 2, similar to the activities of other MT-MMPs, the activity of MT4-MMP(2) was not inhibited by TIMP-1, but strongly inhibited by TIMP-2.

These results revealed that MT4-MMP(2) is one type of MT-MMP.

Table 2. Measurement of the Activity of Human MT4-MMP(2) Partial Peptide (Active Domain)

Sample	Trypsin Treatment	Inhibitor	Fluorescence Intensity (Mean \pm SD) (n=3)
Blank			0.000 \pm 0.057
Human MT4-MMP(2) partial peptide	-	None	1.304 \pm 0.056
Human MT4-MMP(2) partial peptide	+	None	4.882 \pm 0.102
Human MT4-MMP(2) partial peptide	+	TIMP-1	3.493 \pm 0.166
Human MT4-MMP(2) partial peptide	+	TIMP-2	0.076 \pm 0.065

EXAMPLE 9. Cloning of Mouse MT5-MMP Gene

In order to isolate mouse MT5-MMP gene, a brain cDNA library from mouse 17-day embryo was prepared using ZAP-cDNA Synthesis Kit (Stratagene) according to the manual attached to the kit.

The resultant cDNA library was screened by plaque hybridization using human MT3-MMP gene as a probe. Clones exhibiting a strong signal and clones exhibiting a weak signal were obtained. The nucleotide sequences of these clones were determined.

As a result of analysis of clones with a weak signal, a 2.1 kb sequence was found in one of them. Although this sequence exhibited weak homology to human and rat MT3-MMP genes, it was not homologous to other MMP genes. Thus, it was considered that this sequence represents a novel MMP gene.

Subsequently, a 3.7 kb cDNA fragment that hybridized to the above-described 2.1 kb sequence was obtained from the above library by plaque hybridization. From the 2.1 kb and 3.7 kb sequences, a 4.2 kb cDNA sequence shown in SEQ ID NO: 7 was obtained.

A protein with 618 amino acids represented by SEQ ID NO: 5 was encoded in the cDNA shown in SEQ ID NO: 7. Since the peptide of SEQ ID NO: 5 contains those sequences corresponding to the individual domains of MT-MMPs in well-conserved states, it was concluded that this peptide is a novel MT-MMP, namely, mouse MT5-MMP (Fig. 1).

EXAMPLE 10. Cloning of Human MT5-MMP Gene

In order to confirm the human gene corresponding to mouse MT5-MMP gene, a human kidney cDNA library (Clontech) was screened by plaque hybridization using mouse MT5-MMP gene as a probe in the same manner as in Example 9. As a result, a gene that has 92% homology to mouse MT5-MMP gene and is different from known MT-MMP genes was obtained.

All of the sequenced human MT5-MMP cDNA clones lacked a 5' region that is supposed to encode a signal peptide. Thus, the sequence of the missing region was determined by 5' RACE as described below to thereby determine the nucleotide sequence containing the entire region encoding human MT5-MMP gene.

Briefly, cDNA was prepared from a human brain poly(A)⁺ RNA (Clontech) using Superscript II (Gibco BRL) and a human MT5-MMP gene-selective primer (SEQ ID NO: 19) according to the manual attached to the kit.

A single-stranded oligonucleotide adaptor (SEQ ID NO: 10) was ligated to the resultant cDNA with T4 RNA ligase. Then, the cDNA was subjected to PCR in GC buffer using the MT5-MMP gene-selective primer (SEQ ID NO: 19), an adaptor-selective primer (SEQ ID NO: 11) and LA Taq (Takara).

After completion of the above PCR, another PCR was performed using an other gene-selective primer (SEQ ID NO: 20) and an adaptor-selective primer (SEQ ID NO: 13). From the above-mentioned sequence obtained from the human kidney cDNA library using the mouse gene as a probe and the sequence obtained from the 5' RACE, a 2.6 kb cDNA fragment

(shown in SEQ ID NO: 8) that encodes a 645 amino acid protein (shown in SEQ ID NO: 6) was obtained.

EXAMPLE 11. Expression of MT5-MMP mRNAs in Internal Organs

Expression of MT5-MMP gene in tissues was examined by Northern blotting.

Briefly, 20 μ g of total RNA was electrophoresed on 1% agarose gel and transferred onto a nylon membrane. Then, Northern blotting was carried out using 32 P-labeled mouse MT5-MMP gene as a probe to examine the expression pattern of approximately 4 kb MT5-MMP mRNAs.

In 2-week old mice, a strong expression was observed only in the brain, but the expression was around detection limit or below in other tissues of other organs.

When expression in human tissues was examined with Multiple Tissue Blot (Clontech) using human MT5-MMP gene as a probe, high expression was observed in the brain. The results of Northern blotting using 32 P-labeled human MT5-MMP gene as a probe revealed that strong expression of both 4.0 kb and 4.8 kb MT5-MMP mRNAs are also recognized in the human brain. In human, the expression was also recognized in the kidney and pancreas. The 4.8 kb mRNA and the 4.0 kb mRNA were expressed strongly in the brain and in the kidney and pancreas, respectively.

Then, RT-PCR was carried out using MT5-MMP specific primers (SEQ ID NOS: 21 and 22) to analyze these fragments. As a result, it was found that a DNA fragment of the same size as that of the fragment amplified in the brain is amplified in the kidney and pancreas with almost equal efficiencies and that no products of different sizes were found. Thus, it was believed that the shorter transcript contains the entire coding region.

When the expression of MT5-MMP in mouse and human was examined, characteristic expression was observed in the brain. In particular, the expression was limited in the brain in mouse, and was very low in other internal organs.

Since the expression of this gene in the brain is characteristic, site-specific expression was examined using Human Brain Multiple Tissue Blot (Clontech).

High expression of MT5-MMP was observed in the cerebellum. Its expression was

also observed in the cerebral cortex, medulla, occipital region of head, frontal region of head, temporal region of head and putamen, but not observed in the spinal cord.

These results show a remarkable characteristic of MT5-MMP gene different from other MT-MMP genes expressed in various tissues.

In human, the expression of MT5-MMP was ~~also~~ strong in the brain, and its expression was observed in the kidney and pancreas. The results of examination of its site-specific expression in the human brain revealed a characteristic expression in the cerebellum. High expression in the cerebellum was also confirmed in mouse. ✓

These results suggest the possibility that MT5-MMP controls the degradation of extracellular matrixes around cells associated with such processes as the maturation and maintenance of brain tissues, the construction of nervous network, and so forth.

EXAMPLE 12. Expression of MT5-MMP mRNA in Cancer Cells

MT1-MMP is expressed frequently in cancer cells *per se* and interstitial cells around them in many cancer tissues and functions as an activator of gelatinase A at the tissue level. The expression of MT5-MMP in various cancer cell strains was examined by RT-PCR using MT5-MMP-specific primers (SEQ ID NOS: 21 and 22).

The results are shown in Table 3 below.

Table 3. Expression of MT5-MMP Transcript in Cancer Cells

Cancer Cell Line	MT5-MMP	Accession Number
Jurkat (T cell)	-	ATCC TIB-152
Raji (B cell)	-	ATCC CCL-86
BJAB (B cell)	-	ATCC HB-136
THP-1 (monocytic)	-	ATCC TIB-202
K562 (monocytic)	-	ATCC CCL-243
U-937 (monocytic)	-	ATCC CRL-1593.2
U-251 MG (astrocytoma)	-	Hakkoken IFO50288
SK-N-SH (neuroblastoma)	+++	ATCC HTB-11
no.10 (glioma)	++	Hakkoken IFO50368
KALS-1 (glioma)	+++	Hakkoken IFO50434
MKN-7 (gastric)	+	Riken RCB0999
MKN-28 (gastric)	-	Riken RCB1000
NUGC-4 (gastric)	+	HS Found JCRB0834
PANC-1 (pancreatic)	+	ATCC CRL-1469
MIA PaCa-2 (pancreatic)	+	ATCC CRL-1420
SK-HEP-1 (hepatoma)	+	ATCC HTB-52
Hep 3B (hepatoma)	+	ATCC HB-8064
ZR-75-1 (breast)	?	ATCC CRL-1500
MCF7(adenocarcinoma)	-	ATCC HTB-22
T-24 (bladder)	-	ATCC HTB-4
A375 (melanoma)	+/-	ATCC CRL-1619
HT-1080 (fibrosarcoma)	+/-	ATCC CCL-121

+++ : very strong expression; ++ : strong expression; + : medium expression; +/- : slight expression; - : no expression

ATCC: American Type Culture Collection

HS Found.: Japan Health Sciences Foundation

Riken: The Institute of Physical and Chemical Research

Hakkoken: Institute for Fermentation, Osaka

While MT1-MMP is expressed in various cancer cell lines, cell lines expressing MT5-MMP were specific in the nervous system-derived neuroblastoma [SK-N-SH (HTB-11, ATCC)], undifferentiated glioma [no. 10 (IFO50368, Institute for Fermentation, Osaka)], and glioma [KALS-1, (IFO50434, Institute for Fermentation, Osaka)], with the correlation of the expression in brain.

Also, its expression in pancreatic cancer cell strains [PANC-1 (CRL-1469, ATCC); MIA PaCa-2 (CRL-1420, ATCC)] and hepatoma cell strains [SK-HEP-1 (HTB-52, ATCC); Hep 3B (HB-8064, ATCC)] was characteristic.

It is considered that abnormal expression of MT-MMPs on cell surfaces promotes the infiltration of cells. Actually, excessive expression of MT1-MMP enhances the infiltrating ability of cancer cell lines and increases the frequency of experimental metastasis. In human cancer tissues, cancer cells and fibroblasts around them express MT1-MMP at high frequency, and the presence of gelatinase A which MT1-MMP activates at sites of its expression is well correlated with the infiltration and metastasis of cancer.

Since MT5-MMP is expressed in undifferentiated glioma, glioma, pancreatic cancer and hepatoma cell lines, the possibility has been suggested that excessive expression of MT5-MMP is involved in the malignant nature of cancer cells in a specific types of cancers.

EXAMPLE 13. Expression of a Mouse MT5-MMP Partial Peptide (Propeptide Domain + Active Domain) in *E. coli*

A cDNA encoding a mouse MT5-MMP partial peptide having an amino acid sequence represented by positions 40-300 of SEQ ID NO: 5 to which a methionine residue is added at the N terminus was amplified by polymerase chain reaction (PCR) using the cDNA of mouse MT5-MMP as a template.

The amplified fragment was subcloned into an *E. coli* expression vector pET3a (Takara)

and then introduced into *E. coli* BL21 (DE3) pLysS (Takara). This *E. coli* was grown in 1 liter of expression medium (12 g/L of tryptone; 24 g/L of yeast extract; 10 g/L of sodium chloride; 250 mg/L of Tris base; 4 ml/L of glycerol) in the presence of 100 μ g/mL ampicillin until OD₆₀₀ reached 0.5. Then, the cells were stimulated with 0.4 mmol/L isopropyl- β -D-thiogalactopyranoside (IPTG) and cultured for another three hours.

After the culturing, granules (inclusion bodies) consisting of the mouse MT5- MMP partial peptide formed in the *E. coli* cells were recovered by conventional methods and dissolved in a solubilization solution containing 8 mol/L urea, 50 mmol/L Tris-HCl (pH 8.6) and 20 mmol/L dithiothreitol (DTT). The resultant solution was applied to Q-anion ion exchange column followed by recovery of the fraction eluted with 0.1 M NaCl.

This fraction was diluted with a solution containing 50 mmol/L Tris-HCl (pH 8.6), 6 mol/L urea, 1 mmol/L dithiothreitol, 0.15 mol/L sodium chloride, 5 mmol/L calcium chloride, 100 mmol/L zinc chloride and 0.02% sodium azide. Then, cystamine (final concentration: 20 mmol/L) was added to the resultant dilution. Subsequently, the resultant solution was dialyzed against 4 L of a solution containing 50 mmol/L Tris-HCl (pH 8.6), 0.15 mol/L sodium chloride, 5 mmol/L calcium chloride, 100 mmol/L zinc chloride, 5 mmol/L β mercaptoethanol, 1 mmol/L 2-hydroxyethyl disulfide and 0.02% sodium azide at 4°C overnight. Further, dialysis was performed against 10 volumes of a solution containing 50 mmol/L Tris-HCl (pH 7.5), 0.15 mol/L sodium chloride, 5 mmol/L calcium chloride, 50 μ mol/L zinc chloride and 0.02% sodium azide (4 hr x 3 times). The thus dialyzed solution was centrifuged at 22,000xg at 4°C for 10 min to remove the precipitate.

The supernatant obtained was concentrated with Amicon YM-10 (Millipore) and treated with 0.1 μ g/ml trypsin at 37°C for 30 min. After inactivation of the trypsin with 1 mmol/L DTT, the sample was applied to S-200 column pre-equilibrated with a buffer containing 50 mmol/L Tris-HCl (pH 7.5), 150 mmol/L sodium chloride, 10 mmol/L calcium chloride and 0.02% sodium azide to perform gel filtration. As a result, the mouse MT5-MMP partial peptide (propeptide domain + active domain) was obtained.

Human MT5-MMP peptide can also be expressed in the same manner.

EXAMPLE 14. Measurement of the Activity of Mouse MT5-MMP Partial Peptide (Active Domain)

ProMMP-2 (final concentration: 1 μ g/mL) and the mouse MT5-MMP partial peptide (propeptide domain + active domain) (final concentration: 1 μ g/mL) were mixed and incubated at 37°C for 1 hr. In this operation, Brij 35-added TNC buffer [50 mmol/L Tris-HCl (pH 7.5), 150 mmol/L NaCl, 10 mmol/L CaCl₂, 0.02% NaN₃, 0.05% Brij 35] was used. After the incubation, an equal volume of SDS/PAGE loading buffer was added to the sample, which was then electrophoresed and subjected to Coomassie staining according to routine procedures. As a positive control of activation for ProMMP-2, p-aminophenylmercuric acetate (APMA) was used. As a result, activation of ProMMP-2 was recognized depending on a MMP concentration. The results are shown in Fig. 2.

INDUSTRIAL APPLICABILITY

By using the DNA of novel MT4-MMP(2) polypeptide obtained by the present invention, it becomes possible to diagnose, prevent or treat diseases such as arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, wounds including corneal ulcer, leukemia, cancer, and inflammations associated with infiltration of leukocytes.

Furthermore, by using the DNA of novel MT5-MMP polypeptide obtained by the present invention, it becomes possible to diagnose, prevent or treat diseases such as arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, wounds including corneal ulcer, leukemia, brain disorders at the time of cerebral apoplexy, Alzheimer's disease, dementia, multiple sclerosis, Parkinson's disease, brain tumor, cancer, and inflammations associated with infiltration of leukocytes.

CLAIMS

1. A polypeptide consisting of the amino acid sequence as shown in SEQ ID NO: 1.
2. A polypeptide having an amino acid sequence wherein one or several amino acids are deleted, substituted or added in the amino acid sequence of the polypeptide of claim 1 and having metalloproteinase activity.
3. A polypeptide consisting of the amino acid sequence as shown in SEQ ID NO: 2.
4. A polypeptide having an amino acid sequence wherein one or several amino acids are deleted, substituted or added in the amino acid sequence of the polypeptide of claim 3 and having metalloproteinase activity.
5. A polypeptide consisting of the amino acid sequence as shown in SEQ ID NO: 5.
6. A polypeptide having an amino acid sequence wherein one or several amino acids are deleted, substituted or added in the amino acid sequence of the polypeptide of claim 5 and having metalloproteinase activity.
7. A polypeptide consisting of the amino acid sequence as shown in SEQ ID NO: 6.
8. A polypeptide having an amino acid sequence wherein one or several amino acids are deleted, substituted or added in the amino acid sequence of the polypeptide of claim 7 and having metalloproteinase activity.
9. A DNA encoding the polypeptide of any one of claims 1 to 4.
10. A DNA encoding the polypeptide of any one of claims 5 to 8.

11. A DNA consisting of the nucleotide sequence of positions 86-1846 of SEQ ID NO: 3 or positions 100-1917 of SEQ ID NO: 4, or a DNA which hybridizes to said DNA under stringent conditions and which encodes a polypeptide having metalloproteinase activity.
12. A DNA consisting of the nucleotide sequence of positions 75-1928 of SEQ ID NO: 7 or positions 1-1935 of SEQ ID NO: 8, or a DNA which hybridizes to said DNA under stringent conditions and which encodes a polypeptide having metalloproteinase activity.
13. A recombinant DNA that is obtained by integrating the DNA of any one of claims 9 to 12 into a vector.
14. A transformant comprising the recombinant DNA of claim 13.
15. The transformant of claim 14, wherein said transformant is a microorganism belonging to the genus *Escherichia*.
16. The transformant of claim 15, wherein said microorganism belonging to the genus *Escherichia* is *Escherichia coli*.
17. A method of producing the polypeptide of any one of claims 1 to 8, comprising culturing a transformant comprising a recombinant DNA obtained by integrating a DNA encoding said polypeptide into a vector in a medium, allowing said polypeptide to be produced and accumulated in the resultant culture, and recovering said polypeptide from said culture.
18. An oligonucleotide selected from an oligonucleotide having a nucleotide sequence identical with a nucleotide sequence consisting of consecutive 5 to 60 bases of the DNA of claim 9 or 11; an oligonucleotide having a nucleotide sequence complementary to the nucleotide sequence of said oligonucleotide; or an oligonucleotide derivative of any one of the

above oligonucleotides.

19. An oligonucleotide selected from an oligonucleotide having a nucleotide sequence identical with a nucleotide sequence consisting of consecutive 5 to 60 bases of the DNA of claim 10 or 12; an oligonucleotide having a nucleotide sequence complementary to the nucleotide sequence of said oligonucleotide; or an oligonucleotide derivative of any one of the above oligonucleotides.
20. A method of detecting an mRNA encoding the polypeptide of any one of claims 1 to 8 using the oligonucleotide of claim 18 or 19.
21. A method of inhibiting expression of the polypeptide of any one of claims 1 to 8 using the oligonucleotide of claim 18 or 19.
22. A method of screening for an inhibitor or an activator of the polypeptide of any one of claims 1 to 8, which comprises using the polypeptide and a cell that expresses the polypeptide.
23. A diagnostic agent, therapeutic agent or prophylactic agent for arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, wounds, corneal ulcer, tissue injury or inflammations associated with infiltration of leukocytes, wherein said agent comprises the polypeptide of any one of claims 1 to 4.
24. A diagnostic agent, therapeutic agent or prophylactic agent for arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, wounds, corneal ulcer, tissue injury, inflammations associated with infiltration of leukocytes,

brain disorders at the time of cerebral apoplexy, Alzheimer's disease, dementia, multiple sclerosis, Parkinson's disease or brain tumor, wherein said agent comprises the polypeptide of any one of claims 5 to 8.

25. A diagnostic agent, therapeutic agent or prophylactic agent for arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, wounds, corneal ulcer, tissue injury or inflammations associated with infiltration of leukocytes, wherein said agent comprises the DNA of claim 9 or 11.

26. A diagnostic agent, therapeutic agent or prophylactic agent for arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, wounds, corneal ulcer, tissue injury, inflammations associated with infiltration of leukocytes, brain disorders at the time of cerebral apoplexy, Alzheimer's disease, dementia, multiple sclerosis, Parkinson's disease or brain tumor, wherein said agent comprises the DNA of claim 10 or 12.

27. A diagnostic agent, therapeutic agent or prophylactic agent for arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, wounds, corneal ulcer, tissue injury or inflammations associated with infiltration of leukocytes, wherein said agent comprises the oligonucleotide of claim 18.

28. A diagnostic agent, therapeutic agent or prophylactic agent for arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact

dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, wounds, corneal ulcer, tissue injury, inflammations associated with infiltration of leukocytes, brain disorders at the time of cerebral apoplexy, Alzheimer's disease, dementia, multiple sclerosis, Parkinson's disease or brain tumor, wherein said agent comprises the oligonucleotide of claim 19.

29. A vector for gene therapy for treating arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, wounds, corneal ulcer, tissue injury or inflammations associated with infiltration of leukocytes, wherein said vector is obtained by integrating the DNA of claim 9 or 11, or the oligonucleotide of claim 18 into a vector.

30. A vector for gene therapy for treating arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, wounds, corneal ulcer, tissue injury, inflammations associated with infiltration of leukocytes, brain disorders at the time of cerebral apoplexy, Alzheimer's disease, dementia, multiple sclerosis, Parkinson's disease or brain tumor, wherein said vector is obtained by integrating the DNA of claim 10 or 12, or the oligonucleotide of claim 19 into a vector.

31. A method of screening for a compound that regulates the expression of a gene encoding the polypeptide of any one of claims 1 to 8, which comprises contacting a cell that expresses the polypeptide with a test sample.

32. The method of claim 31, wherein said compound that regulates the expression of a gene is detected by determining the amount of mRNA encoding the polypeptide of any one of

claims 1 to 8.

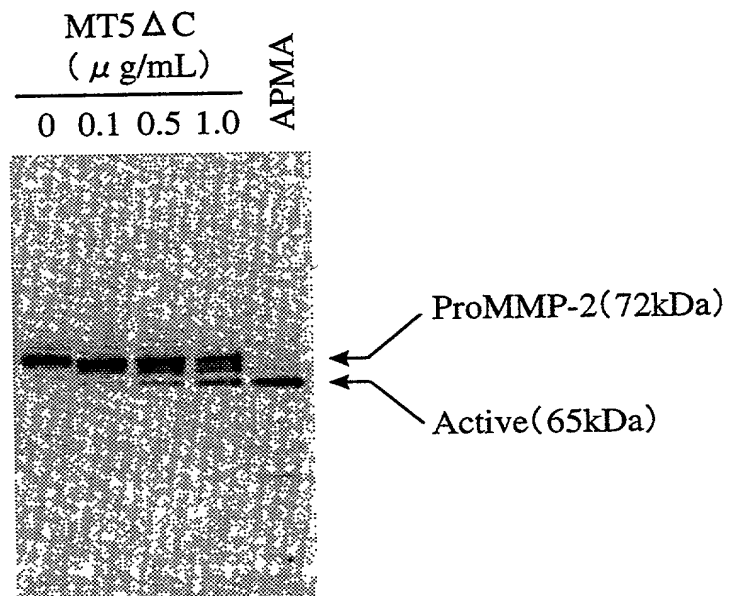
Fig. 1

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human MT1-MMP 1 ---MSPAP---RP-----SRCLLPL-LTLGTALASLGSASQ-----SSFSPEAWLQQYGYLPPGD 49
human MT2-MMP 1 ---MGSDPSAPGRPGWT-----GSLLDREEAARPLLPL-LVLGLCLGLGVAAED-----AEVHAENWRLYGYLPQPS 67
human MT3-MMP 1 -MILLTFSTGRRLDFVH-----HSGVFFLQT-LLWLCAVCG-----TEQYFNVEWMLQYGYLPPPTD 57
human MT4-MMP(2) 1 MRRRAARGPGPP-PPGP-----GLSRLPLPLPLLLALLGTRGGCAAEPPAR-----RAEDLSLGVWLSRFYGLPPAD 69
human MT5-MMP 1 ---MPSRGGRAAPGPPPPPPPGQAPRWSRVRPGRLLLL-LLPALCCLPGAARAAAAAGAGNRAAVAVARADEAEAPFAGQNLKSYGYLLPYD 95
mouse MT5-MMP 1 ---MPSRGGRAAPG-----QASRWSGWRAPGRLLP-LLPALCCLAAAAGAGKPAG-----ADAPFAGQNLKSYGYLLPYE 68
          * * * * *
human MT1-MMP 50 LRHTQSRSPQSLASAAIAAMQKFYGLQVTGKADADTMKAMRRRCGVPDKFGAEIKANVRR--KRYAIQGLKWQHNEITFCIQNYT--PKVGEYATYEAIR 145
human MT2-MMP 68 RHMTMRSQAQILASALAEMQRFYGIPTVGLDEETKEWMKPRCGVPDQFGVRVKANLRRRRKRYALTGRKWNHHLTFSIQNYT--EKLGWYHSMEAVR 165
human MT3-MMP 58 PRMSVLRSAETMQSALAAQQFYGINMTGKVDNRTIDWMKKPRCGVPDQTRGSSKFHIRR--KRYALTGQKWQHKHITYSIKNVT--PKVGDPETRKAIR 153
human MT4-MMP(2) 70 PTTGQLQTQEELSKAITAMQQFGGLEATGILDEATLALMKTPRCSLPDLPLVTQ--ARR--RRQAPATKWNKRNLSWRVTFPRDPSPLGHDVTRALMY 164
human MT5-MMP 96 SRASALHSAKALQSAVSTMQQFYGIPTVGLDQTTIEWMKKPRCGVPDHPHLSR--RRRN--KRYALTGQKWQKHITYSIHNYT--PKVGELDTRKAIR 189
mouse MT5-MMP 69 SRASALHSGKALQSAVSTMQQFYGIPTVGLDQTTIEWMKKPRCGVPDHPHLSR--RRRN--KRYALTGQKWQKHITYSIHNYT--PKVGELDTRKAIR 162
          * * * * *
human MT1-MMP 146 KAFRVWESATPLRFREVPYAYIREGHEKQADIMIFFAEGFHGDSTPFDGEGGFLAHAYFPGP-IGGDTHFDSAEPWTVRNELDNGNDIFLVAHVHELGA 244
human MT2-MMP 166 RAFRVWEQATPLVFQVPEYEDIRLRQKEADIMVLFASGFHGDSSPFDGEGGFLAHAYFPGP-IGGDTHFDSAEPWTVRNELDNGNDIFLVAHVHELGA 264
human MT3-MMP 154 RAFDVWQNVPLTFEEVYSELENGK-RDVTITIFASGFHGDSSPFDGEGGFLAHAYFPGP-IGGDTHFDSAEPWTVRNELDNGNDIFLVAHVHELGA 251
human MT4-MMP(2) 165 YALKVWSDIAPLNFHEV-----AGS--TADIQIDFSKADHNDGYFPDARR-HRAHAFFPGHHTAGYTHFNDEAWTFRSSDAHGMDFLVAHVHEFGHA 255
human MT5-MMP 288 LGLEHSSDPSAIMAPFYQYMETH--NFKLQDDLQGIQKIYGPPAELEPTRLPLTPVRRIHSPSE-RKHERQPRPPPLGD-----368
mouse MT5-MMP 163 QAFDVWQKVPLTFEEVYSELENGK-RDVTITIFASGFHGDSSPFDGEGGFLAHAYFPGP-IGGDTHFDSAEPWTVRNELDNGNDIFLVAHVHELGA 260
          * * * * *
human MT1-MMP 245 LGLEHSSDPSAIMAPFYQWMDTE--NFVLPDDDRRGIQQLYGGESG-----FPTKMPPQP-----RTTSRSPVPDKPKNP-----312
human MT2-MMP 265 LGLEHSSNPNAIMAPFYQWKDVD--NFKLPEDDLQGIQQLYGTDPGQPTQPLPTVTPRRP-----RPDHRPPRPQPPPPGKPERPKPGPPVQPR 357
human MT3-MMP 252 LGLEHSDNPTAIMAPFYQYMETD--NFKLPEDDLQGIQKIYGPPDKIPPTRLPTVPPHRSIPPADPRKNDP-PKPPRPPTG-----331
human MT4-MMP(2) 256 IGLSHVAAHSIMRPFYQGVGDLRYGLPYEDKVRVWQLYGVRESVSTAQ--PEEPPLLE-----PPDNRSSAPPRKD-----329
human MT5-MMP 288 LGLEHSSDPSAIMAPFYQYMETH--NFKLQDDLQGIQKIYGPPAELEPTRLPLTPVRRIHSPSE-RKHERQPRPPPLGD-----368
mouse MT5-MMP 261 LGLEHSDNPSAIMAPFYQYMETH--NFKLQDDLQGIQKIYGPPAELEPTRLPLTPVRRIHSPSE-RKHERQPRPPPLGD-----341
          * * * * *
human MT1-MMP 313 -----TYGPNICDGNFDTVAMLRGEMFVFKRWFVRVRRNNQ-VMDGYPMPIQGFWRGLP--ASINTAYER-KDGKVFVFKGDKHWFDEASLEPGYPK 401
human MT2-MMP 358 ATERPDQYGPNICDGNFDTVAMLRGEMFVFKRWFVRVRRNNQ-VLDNYPMPIGHFWRGLP--GDISAAYER-QDGRFVFFKGDRYWLFRANLEPGYPQ 452
human MT3-MMP 332 -RPSYPGAKPNICDGNFDTLAILRREMVFVKDQFWVRVRRNNQ-VMDGYPMQITYFWRGLP--PSIDAVYEN-SDGNFVFFKGDKYVWFKDTTLQPGYPH 425
human MT4-MMP(2) 330 -----VPHRCSHFDAVAQIRGEAFFKGYFWRLTRDRHLVSLQPAQMHRFWRGLPLHLDSYDAVYERTSDHKIVFFKGDRYVWFKDNVVEEGYPR 421
human MT5-MMP 369 -RPSTPGTKPNICDGNFDTVALFRGEMFVFKDRWFVRLRNNR-VQEGYPMQIEQFWKGLP--ARIDAAYER-ADGRFVFFKGDKYVWFKEVTVEPGYPH 462
mouse MT5-MMP 342 -RPSTPGAKPNICDGNFDTVALFRGEMFVFKDRWFVRLRNNR-VQEGYPMQIEQFWKGLP--ARIDAAYER-ADGRFVFFKGDKYVWFKEVTVEPGYPH 435
          * * * * *
human MT1-MMP 402 HIKEGLRGLPTDKIDAALFWMNGKTYFFRGKNKYRFEELRAVDSEYPPKNIKVWEGIPESPRGSFMSGDEVFTYFYKGNKYKFNQKLKVEPGYPKSA 501
human MT2-MMP 453 PLTSGYGLIPYDRIDTAIWWEPTGHTFFQEDRYWRNEETQGDGPYKPISVWQGIASPQGAFLSNDAAITYFYKGTXYKFNQKLKVEPGYPKSI 552
human MT3-MMP 426 DLITLGSGLIPPHGIDSAIWWEVDGKTYFFKGDRYWRNEETQGDGPYKPIITVWKGIPESPGQAFVHKENGFTYFYKGEYKFNQKLKVEPGYPRSI 525
human MT4-MMP(2) 422 PVSDFS--LPPGIDAAFSWAHNDRTYFFKQDLYWRVDDHTRHMDPGYPAQSPLWRGVPSTLDDAMRWSHG-ASYFFRGQYKWLVDGELEVAPGYPQST 518
human MT5-MMP 463 SLGELGSLCPREGIDTALRWEVPVKTYFFKGERYWCYSEERRATDPGYKPIITVWKGIPQAPQGAFISKEGYTTYFYKGRDYKFNQKLKVEPGYPRNI 562
mouse MT5-MMP 436 SLGELGSLCPREGIDTALRWEVPVKTYFFKGERYWCYSEERRATDPGYKPIITVWKGIPQAPQGAFISKEGYTTYFYKGRDYKFNQKLKVEPGYPRNI 535
          * * * * *
human MT1-MMP 502 LRDMWGCPSGGRPDE-----GTEETEVIIEVDE-----EGGG-----AVSAAAVVLPVLLLLVLAVGLAVFFFRH 565
human MT2-MMP 553 LRDMWGCQEHVEPGRPDPVARPPFNPHGAEAGDAGVDGDDGAGVKNKDGSRVVVQMEEVARTVNVVMPVPLLLLLCVLGLTYALVQMQRK 652
human MT3-MMP 526 LKDFMGCDG-PTDRVKEGH-----SPDDVDIVIKLNTAS-----TVKAIIVIPICILALCLLVYTVFQFKRK 590
human MT4-MMP(2) 519 ARDWLVCGDSQADGSAAGVDAE--GPRAPPQGHQSRSEDGYEVC-----SCTSGASSPPGAPGLVAATMLLLLP--590
human MT5-MMP 563 LRDMWGCNQKEVERRKERR-----LPQDDVDIMVTINDVPG-----SVNAVAVVIPCILSLCILLVYTVFQFKNK 628
mouse MT5-MMP 536 LRDMWGCNQKEVERRKERR-----LPQDDVDIMVTINDVPG-----SVNAVAVVIPCILSLCILLVYTVFQFKNK 601
          * * * * *
human MT1-MMP 566 GTPRRLLYCQRSLDKV 582
human MT2-MMP 653 GAPRVLLYCKRSLQEWV 669
human MT3-MMP 591 GTPRHILYCKRSMQEWV 607
human MT4-MMP(2) 591 LSPGALWTAQAALTL--605
human MT5-MMP 629 TGPQPVTYYKRPVQEWV 645
mouse MT5-MMP 602 AGPQPVTYYKRPVQEWV 618
          * * * * *

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Fig. 2



Attorney's Docket No.: _____

DECLARATION, POWER OF ATTORNEY AND PETITION

I (We), the undersigned inventor(s), hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I (We) believe that I am (we are) the original, first, and joint (sole) inventor(s) of the subject matter which is claimed and for which a patent is sought on the invention entitled

DNAS ENCODING NOVEL POLYPEPTIDES

the specification of which

☐ is attached hereto.

☐ was filed on _____ as

Application Serial No. _____

and amended on _____

☒ was filed as PCT international application

Number PCT/JP99/05349

on September 29, 1999

and was amended under PCT Article 19

on _____ (if applicable).

I (We) hereby state that I (We) have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above; that I (We) do not know and do not believe that this invention was ever known or used before my invention or discovery thereof, or patented or described in any printed publication in any country before my invention or discovery thereof, or more than one year prior to this application, or in public use or on sale in the United States for more than one year prior to this application; that this invention or discovery has not been patented or made the subject of an inventor's certificate in any country foreign to the United States on an application filed by me or my legal representatives or assigns more than twelve months before this application.

I (We) acknowledge the duty to disclose information known to be material to

the patentability of this application as defined in Section 1.56 of Title 37 Code of Federal Regulations.

I (We) hereby claim foreign priority benefits under Section 119(a)-(d) of Title 35 United States Code, of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Application No.	Country	Filing date	Priority claimed	
<u>276258/1998</u>	<u>Japan</u>	<u>September 29, 1998</u>	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
<u>291505/1998</u>	<u>Japan</u>	<u>September 29, 1998</u>	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
_____	_____	_____	<input type="checkbox"/> Yes	<input type="checkbox"/> No
_____	_____	_____	<input type="checkbox"/> Yes	<input type="checkbox"/> No

I hereby claim the benefit under Section 119(e) of Title 35 United States Code, of any United States application(s) listed below.

(Application Number)

(Filing Date)

(Application Number)

(Filing Date)

I (We) hereby claim the benefit under Section 120 of Title 35 United States Code, of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Section 112 of Title 35 United States Code, I (We) acknowledge the duty to disclose material information as defined in Section 1.56(a) of Title 37 Code of Federal Regulations, which occurred between the filing date of the prior application and national or PCT international filing date of this application:

Application Serial No.	Filing Date	Status (pending, patented, abandoned)
_____	_____	_____
_____	_____	_____
_____	_____	_____

And I (We) hereby appoint: Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.,
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 Registration No. 23,098; Herbert H. Mintz, Registration No. 26,691; C. Larry O'Rourke, Registration No.
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 Registration No. 26,331; Bruce C. Zotter, Registration No. 27,680; Dennis P. O'Reilley, Registration No.
27,932; Allen M. Sokal, Registration No. 26,695; Robert D. Bajefsky, Registration No. 25,387; Richard L.
 Stroup, Registration No. 28,478; David W. Hill, Registration No. 28,220; Thomas L. Irving, Registration
 No. 28,619; Charles E. Lipsey, Registration No. 28,165; Thomas W. Winland, Registration No. 27,605;
 Basil J. Lewris, Registration No. 28,818; Martin I. Fuchs, Registration No. 28,508; E. Robert Yoches,
 Registration No. 30,120; Barry W. Graham, Registration No. 29,924; Susan Haberman Griffen,
 Registration No. 30,907; Richard B. Racine, Registration No. 30,415; Thomas H. Jenkins, Registration
 No. 30,857; Robert E. Converse, Jr., Registration No. 27,432; Clair X. Mullen, Jr., Registration No. 20,348;
 Christopher P. Foley, Registration No. 31,354; John C. Paul, Registration No. 30,413; David M. Kelly,
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 No. 32,824; Thomas W. Banks, Registration No. 32,719; M. Paul Barker, Registration No. 32,013; Bryan
 C. Diner, Registration No. 32,409; Christopher P. Isaac, Registration No. 32,616; Andrew C. Sonu,
 Registration No. 33,457; and Dirk D. Thomas, Registration No. 32,600.

I(We) hereby request that all correspondence regarding this application be sent to the firm of
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P. whose Post office address is: 1300 I
Street, N.W., WASHINGTON, D.C. 20005 U.S.A.

I (We) declare further that all statements made herein of my (our) knowledge
 are true and that all statements were made with the knowledge that willful
 false statements and the like so made are punishable by fine or imprisonment,

or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Motoharu SEIKI

NAME OF FIRST SOLE INVENTOR

Motokazu Seki

Signature of Inventor

March 14, 2001

Date _____

Residence: Tokyo, Japan JPX

Citizen of: Japan

Post Office Address:

Koyamadai-jutaku 5-203, 2-5,

Koyamadai, Shinagawa-ku,

Tokyo 142-0061 Japan

SEQUENCE LISTING

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 Arg Asp Ser Pro Leu Gly His Asp Thr Val Arg Ala Leu Met Tyr Tyr
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gcc ctc aag gtc tgg agc gac att gcg ccc ctg aac ttc cac gag gtg 642
 Ala Leu Lys Val Trp Ser Asp Ile Ala Pro Leu Asn Phe His Glu Val
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gcg ggc agc acc gcc gac atc cag atc gac ttc tcc aag gcc gac cat 690
 Ala Gly Ser Thr Ala Asp Ile Gln Ile Asp Phe Ser Lys Ala Asp His
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aac gac ggc tac ccc ttc gac ggc ccc ggc ggc acc gtg gcc cac gcc 738
 Asn Asp Gly Tyr Pro Phe Asp Gly Pro Gly Gly Thr Val Ala His Ala
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ttc ttc ccc ggc cac cac cac acc gcc ggg gac acc cac ttt gac gat 786
 Phe Phe Pro Gly His His His Thr Ala Gly Asp Thr His Phe Asp Asp
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gac gag gcc tgg acc ttc cgc tcc tgc gat gcc cac ggg atg gac ctg 834

Asp Glu Ala Trp Thr Phe Arg Ser Ser Asp Ala His Gly Met Asp Leu
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 Phe Ala Val Ala Val His Glu Phe Gly His Ala Ile Gly Leu Ser His
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gtg gcc gct gca cac tcc atc atg cgg ccg tac tac cag ggc ccg gtg 930
 Val Ala Ala Ala His Ser Ile Met Arg Pro Tyr Tyr Gln Gly Pro Val
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 Gly Asp Pro Leu Arg Tyr Gly Leu Pro Tyr Glu Asp Lys Val Arg Val
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tgg cag ctg tac ggt gtg cgg gag tct gtg tct ccc acg gcg cag ccc 1026
 Trp Gln Leu Tyr Gly Val Arg Glu Ser Val Ser Pro Thr Ala Gln Pro
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gag gag cct ccc ctg ctg ccg gag ccc cca gac aac cgg tcc agc gcc 1074
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 Pro Pro Arg Lys Asp Val Pro His Arg Cys Ser Thr His Phe Asp Ala
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Trp Arg Leu Thr Arg Asp Arg His Leu Val Ser Leu Gln Pro Ala Gln

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atg cac cgc ttc tgg cgg ggc ctg ccg ctg cac ctg gac agc gtg gac 1266

Met His Arg Phe Trp Arg Gly Leu Pro Leu His Leu Asp Ser Val Asp

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Ala Val Tyr Glu Arg Thr Ser Asp His Lys Ile Val Phe Phe Lys Gly

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Tyr Trp Arg Tyr Asp Asp His Thr Arg His Met Asp Pro Gly Tyr Pro

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 Met Arg Trp Ser Asp Gly Ala Ser Tyr Phe Phe Arg Gly Gln Glu Tyr
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 Trp Lys Val Leu Asp Gly Glu Leu Glu Val Ala Pro Gly Tyr Pro Gln
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 Cys Thr Ser Gly Ala Ser Ser Pro Pro Gly Ala Pro Gly Pro Leu Val
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 Ala Ala Thr Met Leu Leu Leu Leu Pro Pro Leu Ser Pro Gly Ala Leu
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Asp Ala Pro Phe Ala Gly Gln Asn Trp Leu Lys Ser Tyr Gly Tyr Leu
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Leu Pro Tyr Glu Ser Arg Ala Ser Ala Leu His Ser Gly Lys Ala Leu
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Gln Ser Ala Val Ser Thr Met Gln Gln Phe Tyr Gly Ile Pro Val Thr
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Gly Val Leu Asp Gln Thr Thr Ile Glu Trp Met Lys Lys Pro Arg Cys
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Gly Val Pro Asp His Pro His Leu Ser Arg Arg Arg Arg Asn Lys Arg
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Tyr Ala Leu Thr Gly Gln Lys Trp Arg Gln Lys His Ile Thr Tyr Ser

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140

Ile His Asn Tyr Thr Pro Lys Val Gly Glu Leu Asp Thr Arg Lys Ala

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150

155

160

Ile Arg Gln Ala Phe Asp Val Trp Gln Lys Val Thr Pro Leu Thr Phe

165

170

175

Glu Glu Val Pro Tyr His Glu Ile Lys Ser Asp Arg Lys Glu Ala Asp

180

185

190

Ile Met Ile Phe Phe Ala Ser Gly Phe His Gly Asp Ser Ser Pro Phe

195

200

205

Asp Gly Glu Gly Gly Phe Leu Ala His Ala Tyr Phe Pro Gly Pro Gly

210

215

220

Ile Gly Gly Asp Thr His Phe Asp Ser Asp Glu Pro Trp Thr Leu Gly

225

230

235

240

Asn Ala Asn His Asp Gly Asn Asp Leu Phe Leu Val Ala Val His Glu

245

250

255

Leu Gly His Ala Leu Gly Leu Glu His Ser Asn Asp Pro Ser Ala Ile

260

265

270

Met Ala Pro Phe Tyr Gln Tyr Met Glu Thr His Asn Phe Lys Leu Pro

275

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Gln Asp Asp Leu Gln Gly Ile Gln Lys Ile Tyr Gly Pro Pro Ala Glu
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Pro Leu Glu Pro Thr Arg Pro Leu His Thr Leu Pro Val Arg Arg Ile
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His Ser Pro Ser Glu Arg Lys His Glu Arg His Pro Arg Pro Pro Arg
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Pro Pro Leu Gly Asp Arg Pro Ser Thr Pro Gly Ala Lys Pro Asn Ile
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Cys Asp Gly Asn Phe Asn Thr Val Ala Leu Phe Arg Gly Glu Met Phe
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Val Phe Lys Asp Arg Trp Phe Trp Arg Leu Arg Asn Asn Arg Val Gln
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Glu Gly Tyr Pro Met Gln Ile Glu Gln Phe Trp Lys Gly Leu Pro Ala
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Lys Gly Asp Lys Tyr Trp Val Phe Lys Glu Val Thr Val Glu Pro Gly
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Tyr Pro His Ser Leu Gly Glu Leu Gly Ser Cys Leu Pro Arg Glu Gly
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Lys Gly Arg Asp Tyr Trp Lys Phe Asp Asn Gln Lys Leu Ser Val Glu
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Pro Gly Tyr Pro Arg Asn Ile Leu Arg Asp Trp Met Gly Cys Lys Gln
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Lys Glu Val Glu Arg Arg Lys Glu Arg Arg Leu Pro Gln Asp Asp Val
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Ala Ala Arg Ala Ala Ala Ala Ala Ala Gly Ala Gly Asn Arg Ala Ala

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Val Ala Val Ala Val Ala Arg Ala Asp Glu Ala Glu Ala Pro Phe Ala

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Gly Gln Asn Trp Leu Lys Ser Tyr Gly Tyr Leu Leu Pro Tyr Asp Ser

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Thr Thr Ile Glu Trp Met Lys Lys Pro Arg Cys Gly Val Pro Asp His
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Pro His Leu Ser Arg Arg Arg Arg Asn Lys Arg Tyr Ala Leu Thr Gly
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Gln Lys Trp Arg Gln Lys His Ile Thr Tyr Ser Ile His Asn Tyr Thr
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Pro Lys Val Gly Glu Leu Asp Thr Arg Lys Ala Ile Arg Gln Ala Phe
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Asp Val Trp Gln Lys Val Thr Pro Leu Thr Phe Glu Glu Val Pro Tyr
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His Glu Ile Lys Ser Asp Arg Lys Glu Ala Asp Ile Met Ile Phe Phe
210 215 220

Ala Ser Gly Phe His Gly Asp Ser Ser Pro Phe Asp Gly Glu Gly Gly
225 230 235 240

Phe Leu Ala His Ala Tyr Phe Pro Gly Pro Gly Ile Gly Gly Asp Thr
245 250 255

His Phe Asp Ser Asp Glu Pro Trp Thr Leu Gly Asn Ala Asn His Asp
260 265 270

Gly Asn Asp Leu Phe Leu Val Ala Val His Glu Leu Gly His Ala Leu
275 280 285

Gly Leu Glu His Ser Ser Asp Pro Ser Ala Ile Met Ala Pro Phe Tyr
290 295 300

Gln Tyr Met Glu Thr His Asn Phe Lys Leu Pro Gln Asp Asp Leu Gln
305 310 315 320

Gly Ile Gln Lys Ile Tyr Gly Pro Pro Ala Glu Pro Leu Glu Pro Thr
325 330 335

Arg Pro Leu Pro Thr Leu Pro Val Arg Arg Ile His Ser Pro Ser Glu
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Arg Lys His Glu Arg Gln Pro Arg Pro Pro Arg Pro Pro Leu Gly Asp
355 360 365

Arg Pro Ser Thr Pro Gly Thr Lys Pro Asn Ile Cys Asp Gly Asn Phe
370 375 380

Asn Thr Val Ala Leu Phe Arg Gly Glu Met Phe Val Phe Lys Asp Arg
385 390 395 400

Trp Phe Trp Arg Leu Arg Asn Asn Arg Val Gln Glu Gly Tyr Pro Met

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410

415

Gln Ile Glu Gln Phe Trp Lys Gly Leu Pro Ala Arg Ile Asp Ala Ala

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425

430

Tyr Glu Arg Ala Asp Gly Arg Phe Val Phe Phe Lys Gly Asp Lys Tyr

435

440

445

Trp Val Phe Lys Glu Val Thr Val Glu Pro Gly Tyr Pro His Ser Leu

450

455

460

Gly Glu Leu Gly Ser Cys Leu Pro Arg Glu Gly Ile Asp Thr Ala Leu

465

470

475

480

Arg Trp Glu Pro Val Gly Lys Thr Tyr Phe Phe Lys Gly Glu Arg Tyr

485

490

495

Trp Arg Tyr Ser Glu Glu Arg Arg Ala Thr Asp Pro Gly Tyr Pro Lys

500

505

510

Pro Ile Thr Val Trp Lys Gly Ile Pro Gln Ala Pro Gln Gly Ala Phe

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Ile Ser Lys Glu Gly Tyr Tyr Thr Tyr Phe Tyr Lys Gly Arg Asp Tyr

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Trp Lys Phe Asp Asn Gln Lys Leu Ser Val Glu Pro Gly Tyr Pro Arg

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555

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Asn Ile Leu Arg Asp Trp Met Gly Cys Asn Gln Lys Glu Val Glu Arg
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Ile Asn Asp Val Pro Gly Ser Val Asn Ala Val Ala Val Val Ile Pro
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Cys Ile Leu Ser Leu Cys Ile Leu Val Leu Val Tyr Thr Ile Phe Gln
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Met Pro Arg Ser Arg Gly Gly Arg Ala Ala Pro Gly

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Gln Ala Ser Arg Trp Ser Gly Trp Arg Ala Pro Gly Arg Leu Leu Pro

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ctg ctg ccc gcg ctc tgc tgc ctc gcg gcg gcg gcg ggg gcc ggg aag 206

Leu Leu Pro Ala Leu Cys Cys Leu Ala Ala Ala Ala Gly Ala Gly Lys

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ccg gcc ggg gcg gac gcg ccc ttc gct ggg cag aac tgg tta aaa tca 254

Pro Ala Gly Ala Asp Ala Pro Phe Ala Gly Gln Asn Trp Leu Lys Ser

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Tyr Gly Tyr Leu Leu Pro Tyr Glu Ser Arg Ala Ser Ala Leu His Ser

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Gly Lys Ala Leu Gln Ser Ala Val Ser Thr Met Gln Gln Phe Tyr Gly

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85

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Ile Pro Val Thr Gly Val Leu Asp Gln Thr Thr Ile Glu Trp Met Lys

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 Lys Pro Arg Cys Gly Val Pro Asp His Pro His Leu Ser Arg Arg Arg
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 Arg Asn Lys Arg Tyr Ala Leu Thr Gly Gln Lys Trp Arg Gln Lys His
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 Ile Thr Tyr Ser Ile His Asn Tyr Thr Pro Lys Val Gly Glu Leu Asp
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aca cgg aag gct att cgt cag gct ttc gat gtg tgg cag aag gtg act 590
 Thr Arg Lys Ala Ile Arg Gln Ala Phe Asp Val Trp Gln Lys Val Thr
 160 165 170

cca ctg acc ttt gaa gag gtg cca tac cat gag atc aaa agt gac cgg 638
 Pro Leu Thr Phe Glu Glu Val Pro Tyr His Glu Ile Lys Ser Asp Arg
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aag gag gca gac atc atg atc ttc ttt gct tct ggt ttc cat ggt gac 686
 Lys Glu Ala Asp Ile Met Ile Phe Phe Ala Ser Gly Phe His Gly Asp
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agc tcc cca ttt gat ggg gaa ggg gga ttc cta gcc cat gcc tac ttt 734
 Ser Ser Pro Phe Asp Gly Glu Gly Gly Phe Leu Ala His Ala Tyr Phe
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Pro Gly Pro Gly Ile Gly Gly Asp Thr His Phe Asp Ser Asp Glu Pro
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 Trp Thr Leu Gly Asn Ala Asn His Asp Gly Asn Asp Leu Phe Leu Val
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 Ala Val His Glu Leu Gly His Ala Leu Gly Leu Glu His Ser Asn Asp
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 Pro Ser Ala Ile Met Ala Pro Phe Tyr Gln Tyr Met Glu Thr His Asn
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 Phe Lys Leu Pro Gln Asp Asp Leu Gln Gly Ile Gln Lys Ile Tyr Gly
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 Val Arg Arg Ile His Ser Pro Ser Glu Arg Lys His Glu Arg His Pro
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ctg agc gtg gag cca ggc tac cca cgc aac atc ctg cgt gac tgg atg 1694
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Ser	Met	Leu	Asp	Asp	Ala	Met	Arg	Trp	Ser	Asp	Gly	Ala	Ser	Tyr	Phe
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Leu	Pro	Pro	Ala	Asp	Pro	Thr	Thr	Gly	Gln	Leu	Gln	Thr	Gln	Glu	Glu	65	70	75	80
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His	Gly	Met	Asp	Leu	Phe	Ala	Val	Ala	Val	His	Glu	Phe	Gly	His	Ala	245	250	255	
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Tyr	Gln	Gly	Pro	Val	Gly	Asp	Pro	Leu	Arg	Tyr	Gly	Leu	Pro	Tyr	Glu	275	280	285	
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Pro	Thr	Ala	Gln	Pro	Glu	Glu	Pro	Pro	Leu	Leu	Pro	Glu	Pro	Pro	Asp	305	310	315	320
Asn	Arg	Ser	Ser	Ala	Pro	Pro	Arg	Lys	Asp	Val	Pro	His	Arg	Cys	Ser	325	330	335	
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350

Lys Gly Lys Tyr Phe Trp Arg Leu Thr Arg Asp Arg His Leu Val Ser
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Leu Gln Pro Ala Gln Met His Arg Phe Trp Arg Gly Leu Pro Leu His
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Leu Asp Ser Val Asp Ala Val Tyr Glu Arg Thr Ser Asp His Lys Ile
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Val Phe Phe Lys Gly Asp Arg Tyr Trp Val Phe Lys Asp Asn Asn Val
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Glu Glu Gly Tyr Pro Arg Pro Val Ser Asp Phe Ser Leu Pro Pro Gly
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Gly Ile Asp Ala Ala Phe Ser Trp Ala His Asn Asp Arg Thr Tyr Phe
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Arg Gly Gln Glu Tyr Trp Lys Val Leu Asp Gly Glu Leu Glu Val Ala
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Tyr Glu Val Cys Ser Cys Thr Ser Gly Ala Ser Ser Pro Pro Gly Ala
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Ser Pro Arg Gly Pro Gly Pro Pro Arg Pro Gly Pro Gly Leu Pro Pro
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Ala Pro Arg Ala Glu Asp Leu Ser Leu Gly Val Glu Trp Leu Ser Arg
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Phe Gly Tyr Leu Pro Pro Ala Asp Pro Ala Ser Gly Gln Leu Gln Thr
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Thr Pro Arg Cys Ser Leu Pro Asp Leu Pro Pro Gly Ala Gln Ser Arg
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370

375

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570

575

580

585

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Thr Ala Met Gln Gln Phe Gly Gly Leu Glu Ala Thr Gly Ile Leu Asp
90 95 100

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Glu Ala Thr Leu Ala Leu Met Lys Thr Pro Arg Cys Ser Leu Pro Asp
105 110 115

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Arg	Asp	Ser	Pro	Leu	Gly	His	Asp	Thr	Val	Arg	Ala	Leu	Met	Tyr	Tyr	
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Asp	Glu	Ala	Trp	Thr	Phe	Arg	Ser	Ser	Asp	Ala	His	Gly	Met	Asp	Leu	
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Trp	Arg	Leu	Thr	Arg	Asp	Arg	His	Leu	Val	Ser	Leu	Gln	Pro	Ala	Gln	
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Met	His	Arg	Phe	Trp	Arg	Gly	Leu	Pro	Leu	His	Leu	Asp	Ser	Val	Asp	
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Asp	Arg	Tyr	Trp	Val	Phe	Lys	Asp	Asn	Asn	Val	Glu	Glu	Gly	Tyr	Pro	
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Tyr	Trp	Arg	Tyr	Asp	Asp	His	Thr	Arg	His	Met	Asp	Pro	Gly	Tyr	Pro	
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Ala	Gln	Ser	Pro	Leu	Trp	Arg	Gly	Val	Pro	Ser	Thr	Leu	Asp	Asp	Ala	
470				475					480						485	
atg	cgc	tgg	tcc	gac	ggg	gcc	tcc	tac	ttc	ttc	cgt	ggc	cag	gag	tac	1602
Met	Arg	Trp	Ser	Asp	Gly	Ala	Ser	Tyr	Phe	Phe	Arg	Gly	Gln	Glu	Tyr	
			490					495						500		
tgg	aaa	gtg	ctg	gat	ggc	gag	ctg	gag	gtg	gca	ccc	ggg	tac	cca	cag	1650
Trp	Lys	Val	Leu	Asp	Gly	Glu	Leu	Glu	Val	Ala	Pro	Gly	Tyr	Pro	Gln	
			505					510					515			
tcc	acg	gcc	cgg	gac	tgg	ctg	gtg	tgt	gga	gac	tca	cag	gcc	gat	gga	1698
Ser	Thr	Ala	Arg	Asp	Trp	Leu	Val	Cys	Gly	Asp	Ser	Gln	Ala	Asp	Gly	
		520					525					530				

tct	gtg	gct	gcg	ggc	gtg	gac	gcg	gca	gag	ggg	ccc	cgc	gcc	cct	cca	1746
Ser	Val	Ala	Ala	Gly	Val	Asp	Ala	Ala	Glu	Gly	Pro	Arg	Ala	Pro	Pro	
	535					540					545					

gga	caa	cat	gac	cag	agc	cgc	tcg	gag	gac	ggg	tac	gag	gtc	tgc	tca	1794
Gly	Gln	His	Asp	Gln	Ser	Arg	Ser	Glu	Asp	Gly	Tyr	Glu	Val	Cys	Ser	
550					555					560					565	

tgc	acc	tct	ggg	gca	tcc	tct	ccc	ccg	ggg	gcc	cca	ggc	cca	ctg	gtg	1842
Cys	Thr	Ser	Gly	Ala	Ser	Ser	Pro	Pro	Gly	Ala	Pro	Gly	Pro	Leu	Val	
				570					575					580		

gct	gcc	acc	atg	ctg	ctg	ctg	ctg	ccg	cca	ctg	tca	cca	ggc	gcc	ctg	1890
Ala	Ala	Thr	Met	Leu	Leu	Leu	Leu	Pro	Pro	Leu	Ser	Pro	Gly	Ala	Leu	
			585					590					595			

tgg	aca	gcg	gcc	cag	gcc	ctg	acg	cta	tgacacacag	cgcgagccca	1937
Trp	Thr	Ala	Ala	Gln	Ala	Leu	Thr	Leu			
	600					605					

tgagaggaca	gaggcggtgg	gacagcctgg	ccacagaggg	caaggactgt	gccggagtcc	1997
ctggggggagg	tgctggcgcg	ggatgaggac	gggccaccct	ggcaccggaa	ggccagcaga	2057
gggcacggcc	cgccagggct	gggcaggctc	aggtggcaag	gacggagctg	tcccctagtg	2117
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cgccaccgcc	ccagcctcct	ccggccctgg	agggagcatc	tcgggctggg	ggcccacccc	2237
tcctgtgcc	ggcgccacca	accccaccca	cactgctgcc	tggtgctccc	gccggcccac	2297
agggcctccg	tccccaggtc	cccagtgggg	cagccctccc	cacagacgag	ccccccacat	2357
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 <212> PRT
 <213> Mouse

<400> 5
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Trp Ser Gly Trp Arg Ala Pro Gly Arg Leu Leu Pro Leu Leu Pro Ala
20 25 30
Leu Cys Cys Leu Ala Ala Ala Ala Gly Ala Gly Lys Pro Ala Gly Ala

35					40					45					
Asp	Ala	Pro	Phe	Ala	Gly	Gln	Asn	Trp	Leu	Lys	Ser	Tyr	Gly	Tyr	Leu
	50					55					60				
Leu	Pro	Tyr	Glu	Ser	Arg	Ala	Ser	Ala	Leu	His	Ser	Gly	Lys	Ala	Leu
65					70					75					80
Gln	Ser	Ala	Val	Ser	Thr	Met	Gln	Gln	Phe	Tyr	Gly	Ile	Pro	Val	Thr
				85					90					95	
Gly	Val	Leu	Asp	Gln	Thr	Thr	Ile	Glu	Trp	Met	Lys	Lys	Pro	Arg	Cys
			100					105					110		
Gly	Val	Pro	Asp	His	Pro	His	Leu	Ser	Arg	Arg	Arg	Arg	Asn	Lys	Arg
		115					120					125			
Tyr	Ala	Leu	Thr	Gly	Gln	Lys	Trp	Arg	Gln	Lys	His	Ile	Thr	Tyr	Ser
	130					135					140				
Ile	His	Asn	Tyr	Thr	Pro	Lys	Val	Gly	Glu	Leu	Asp	Thr	Arg	Lys	Ala
145					150					155					160
Ile	Arg	Gln	Ala	Phe	Asp	Val	Trp	Gln	Lys	Val	Thr	Pro	Leu	Thr	Phe
				165					170					175	
Glu	Glu	Val	Pro	Tyr	His	Glu	Ile	Lys	Ser	Asp	Arg	Lys	Glu	Ala	Asp
			180					185					190		
Ile	Met	Ile	Phe	Phe	Ala	Ser	Gly	Phe	His	Gly	Asp	Ser	Ser	Pro	Phe
		195					200					205			
Asp	Gly	Glu	Gly	Gly	Phe	Leu	Ala	His	Ala	Tyr	Phe	Pro	Gly	Pro	Gly
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Ile	Gly	Gly	Asp	Thr	His	Phe	Asp	Ser	Asp	Glu	Pro	Trp	Thr	Leu	Gly
225					230					235					240
Asn	Ala	Asn	His	Asp	Gly	Asn	Asp	Leu	Phe	Leu	Val	Ala	Val	His	Glu
				245					250					255	
Leu	Gly	His	Ala	Leu	Gly	Leu	Glu	His	Ser	Asn	Asp	Pro	Ser	Ala	Ile
			260					265					270		
Met	Ala	Pro	Phe	Tyr	Gln	Tyr	Met	Glu	Thr	His	Asn	Phe	Lys	Leu	Pro
		275					280					285			
Gln	Asp	Asp	Leu	Gln	Gly	Ile	Gln	Lys	Ile	Tyr	Gly	Pro	Pro	Ala	Glu
	290					295					300				
Pro	Leu	Glu	Pro	Thr	Arg	Pro	Leu	His	Thr	Leu	Pro	Val	Arg	Arg	Ile
305					310					315					320

His Ser Pro Ser Glu Arg Lys His Glu Arg His Pro Arg Pro Pro Arg
 325 330 335
 Pro Pro Leu Gly Asp Arg Pro Ser Thr Pro Gly Ala Lys Pro Asn Ile
 340 345 350
 Cys Asp Gly Asn Phe Asn Thr Val Ala Leu Phe Arg Gly Glu Met Phe
 355 360 365
 Val Phe Lys Asp Arg Trp Phe Trp Arg Leu Arg Asn Asn Arg Val Gln
 370 375 380
 Glu Gly Tyr Pro Met Gln Ile Glu Gln Phe Trp Lys Gly Leu Pro Ala
 385 390 395 400
 Arg Ile Asp Ala Ala Tyr Glu Arg Ala Asp Gly Arg Phe Val Phe Phe
 405 410 415
 Lys Gly Asp Lys Tyr Trp Val Phe Lys Glu Val Thr Val Glu Pro Gly
 420 425 430
 Tyr Pro His Ser Leu Gly Glu Leu Gly Ser Cys Leu Pro Arg Glu Gly
 435 440 445
 Ile Asp Thr Ala Leu Arg Trp Glu Pro Val Gly Lys Thr Tyr Phe Phe
 450 455 460
 Lys Gly Glu Arg Tyr Trp Arg Tyr Ser Glu Glu Arg Arg Ala Thr Asp
 465 470 475 480
 Pro Gly Tyr Pro Lys Pro Ile Thr Val Trp Lys Gly Ile Pro Gln Ala
 485 490 495
 Pro Gln Gly Ala Phe Ile Ser Lys Glu Gly Tyr Tyr Thr Tyr Phe Tyr
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 Lys Gly Arg Asp Tyr Trp Lys Phe Asp Asn Gln Lys Leu Ser Val Glu
 515 520 525
 Pro Gly Tyr Pro Arg Asn Ile Leu Arg Asp Trp Met Gly Cys Lys Gln
 530 535 540
 Lys Glu Val Glu Arg Arg Lys Glu Arg Arg Leu Pro Gln Asp Asp Val
 545 550 555 560
 Asp Ile Met Val Thr Ile Asp Asp Val Pro Gly Ser Val Asn Ala Val
 565 570 575
 Ala Val Val Val Pro Cys Thr Leu Ser Leu Cys Leu Leu Val Leu Leu
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 Tyr Thr Ile Phe Gln Phe Lys Asn Lys Ala Gly Pro Gln Pro Val Thr

595

600

605

Tyr Tyr Lys Arg Pro Val Gln Glu Trp Val
610 615

<210> 6

<211> 645

<212> PRT

<213> Homo sapiens

<400> 6

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Gly Arg Leu Leu Leu Leu Leu Leu Pro Ala Leu Cys Cys Leu Pro Gly
35 40 45

Ala Ala Arg Ala Ala Ala Ala Ala Ala Gly Ala Gly Asn Arg Ala Ala
50 55 60

Val Ala Val Ala Val Ala Arg Ala Asp Glu Ala Glu Ala Pro Phe Ala
65 70 75 80

Gly Gln Asn Trp Leu Lys Ser Tyr Gly Tyr Leu Leu Pro Tyr Asp Ser
85 90 95

Arg Ala Ser Ala Leu His Ser Ala Lys Ala Leu Gln Ser Ala Val Ser
100 105 110

Thr Met Gln Gln Phe Tyr Gly Ile Pro Val Thr Gly Val Leu Asp Gln
115 120 125

Thr Thr Ile Glu Trp Met Lys Lys Pro Arg Cys Gly Val Pro Asp His
130 135 140

Pro His Leu Ser Arg Arg Arg Arg Asn Lys Arg Tyr Ala Leu Thr Gly
145 150 155 160

Gln Lys Trp Arg Gln Lys His Ile Thr Tyr Ser Ile His Asn Tyr Thr
165 170 175

Pro Lys Val Gly Glu Leu Asp Thr Arg Lys Ala Ile Arg Gln Ala Phe
180 185 190

Asp Val Trp Gln Lys Val Thr Pro Leu Thr Phe Glu Glu Val Pro Tyr
195 200 205

His Glu Ile Lys Ser Asp Arg Lys Glu Ala Asp Ile Met Ile Phe Phe
210 215 220

Ala Ser Gly Phe His Gly Asp Ser Ser Pro Phe Asp Gly Glu Gly Gly
 225 230 235 240
 Phe Leu Ala His Ala Tyr Phe Pro Gly Pro Gly Ile Gly Gly Asp Thr
 245 250 255
 His Phe Asp Ser Asp Glu Pro Trp Thr Leu Gly Asn Ala Asn His Asp
 260 265 270
 Gly Asn Asp Leu Phe Leu Val Ala Val His Glu Leu Gly His Ala Leu
 275 280 285
 Gly Leu Glu His Ser Ser Asp Pro Ser Ala Ile Met Ala Pro Phe Tyr
 290 295 300
 Gln Tyr Met Glu Thr His Asn Phe Lys Leu Pro Gln Asp Asp Leu Gln
 305 310 315 320
 Gly Ile Gln Lys Ile Tyr Gly Pro Pro Ala Glu Pro Leu Glu Pro Thr
 325 330 335
 Arg Pro Leu Pro Thr Leu Pro Val Arg Arg Ile His Ser Pro Ser Glu
 340 345 350
 Arg Lys His Glu Arg Gln Pro Arg Pro Pro Arg Pro Pro Leu Gly Asp
 355 360 365
 Arg Pro Ser Thr Pro Gly Thr Lys Pro Asn Ile Cys Asp Gly Asn Phe
 370 375 380
 Asn Thr Val Ala Leu Phe Arg Gly Glu Met Phe Val Phe Lys Asp Arg
 385 390 395 400
 Trp Phe Trp Arg Leu Arg Asn Asn Arg Val Gln Glu Gly Tyr Pro Met
 405 410 415
 Gln Ile Glu Gln Phe Trp Lys Gly Leu Pro Ala Arg Ile Asp Ala Ala
 420 425 430
 Tyr Glu Arg Ala Asp Gly Arg Phe Val Phe Phe Lys Gly Asp Lys Tyr
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 Trp Val Phe Lys Glu Val Thr Val Glu Pro Gly Tyr Pro His Ser Leu
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 Gly Glu Leu Gly Ser Cys Leu Pro Arg Glu Gly Ile Asp Thr Ala Leu
 465 470 475 480
 Arg Trp Glu Pro Val Gly Lys Thr Tyr Phe Phe Lys Gly Glu Arg Tyr
 485 490 495
 Trp Arg Tyr Ser Glu Glu Arg Arg Ala Thr Asp Pro Gly Tyr Pro Lys

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Ile	Ser	Lys	Glu	Gly	Tyr	Tyr	Thr	Tyr	Phe	Tyr	Lys	Gly	Arg	Asp	Tyr
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Trp	Lys	Phe	Asp	Asn	Gln	Lys	Leu	Ser	Val	Glu	Pro	Gly	Tyr	Pro	Arg
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Asn	Ile	Leu	Arg	Asp	Trp	Met	Gly	Cys	Asn	Gln	Lys	Glu	Val	Glu	Arg
				565					570					575	
Arg	Lys	Glu	Arg	Arg	Leu	Pro	Gln	Asp	Asp	Val	Asp	Ile	Met	Val	Thr
			580					585					590		
Ile	Asn	Asp	Val	Pro	Gly	Ser	Val	Asn	Ala	Val	Ala	Val	Val	Ile	Pro
		595					600					605			
Cys	Ile	Leu	Ser	Leu	Cys	Ile	Leu	Val	Leu	Val	Tyr	Thr	Ile	Phe	Gln
	610					615					620				
Phe	Lys	Asn	Lys	Thr	Gly	Pro	Gln	Pro	Val	Thr	Tyr	Tyr	Lys	Arg	Pro
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Val	Gln	Glu	Trp	Val											
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 <212> DNA
 <213> Mouse

<220>
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 Met Pro Arg Ser Arg Gly Gly Arg Ala Ala Pro Gly
 1 5 10
 cag gcc tcg cgc tgg agc ggc tgg cgg gcc ccg ggg cgg ctg ctg ccg 158
 Gln Ala Ser Arg Trp Ser Gly Trp Arg Ala Pro Gly Arg Leu Leu Pro
 15 20 25
 ctg ctg ccc gcg ctc tgc tgc ctc gcg gcg gcg gcg ggg gcc ggg aag 206
 Leu Leu Pro Ala Leu Cys Cys Leu Ala Ala Ala Ala Gly Ala Gly Lys
 30 35 40

ccg Pro 45	gcc Ala	ggg Gly	gcg Ala	gac Asp	gcg Ala 50	ccc Pro	ttc Phe	gct Ala	ggg Gly 55	cag Gln	aac Asn	tgg Trp	tta Leu	aaa Lys	tca Ser 60	254
tat Tyr	ggc Gly	tat Tyr	ctg Leu	ctt Leu 65	ccc Pro	tat Tyr	gag Glu	tcg Ser	cg Arg 70	gca Ala	tct Ser	gcg Ala	ttg Leu	cat His 75	tct Ser	302
ggg Gly	aag Lys	gcc Ala	ttg Leu 80	cag Gln	tcc Ser	gcg Ala	gtc Val	tcc Ser 85	act Thr	atg Met	cag Gln	cag Gln	ttt Phe 90	tac Tyr	ggg Gly	350
atc Ile	cca Pro	gtc Val 95	acc Thr	ggt Gly	gtg Val	ttg Leu	gat Asp 100	cag Gln	aca Thr	aca Thr	atc Ile	gag Glu 105	tgg Trp	atg Met	aag Lys	398
aaa Lys 110	cct Pro	cga Arg	tgt Cys	ggc Gly	gtc Val	cct Pro 115	gat Asp	cat His	ccc Pro	cac His	ttg Leu 120	agc Ser	agg Arg	agg Arg	agg Arg	446
aga Arg 125	aat Asn	aag Lys	cga Arg	tat Tyr	gcc Ala 130	cta Leu	act Thr	gga Gly	cag Gln	aag Lys 135	tgg Trp	agg Arg	cag Gln	aaa Lys	cac His 140	494
atc Ile 145	acc Thr	tac Tyr	agc Ser	att Ile 145	cac His	aat Asn	tat Tyr	acc Thr	cca Pro 150	aag Lys	gtg Val	ggg Gly	gag Glu	ctg Leu 155	gac Asp	542
aca Thr 160	cgg Arg	aag Lys	gct Ala 160	att Ile	cgt Arg	cag Gln	gct Ala	ttc Phe 165	gat Asp	gtg Val	tgg Trp	cag Gln	aag Lys 170	gtg Val	act Thr	590
cca Pro 175	ctg Leu	acc Thr	ttt Phe	gaa Glu	gag Glu	gtg Val	cca Pro 180	tac Tyr	cat His	gag Glu	atc Ile	aaa Lys 185	agt Ser	gac Asp	cgg Arg	638
aag Lys 190	gag Glu	gca Ala	gac Asp	atc Ile	atg Met	atc Ile	ttc Phe 195	ttt Phe	gct Ala	tct Ser	ggg Gly 200	ttc Phe	cat His	ggg Gly	gac Asp	686
agc Ser 205	tcc Ser	cca Pro	ttt Phe	gat Asp	ggg Gly 210	gaa Glu	ggg Gly	gga Gly	ttc Phe	cta Leu 215	gcc Ala	cat His	gcc Ala	tac Tyr	ttt Phe 220	734
cct Pro	ggc Gly	cca Pro	ggg Gly	atc Ile 225	gga Gly	gga Gly	gac Asp	act Thr	cac His 230	ttt Phe	gat Asp	tca Ser	gat Asp	gaa Glu 235	ccc Pro	782
tgg Trp	acg Thr	cta Leu	gga Gly 240	aat Asn	gcc Ala	aac Asn	cat His	gat Asp 245	ggc Gly	aat Asn	gac Asp	ctc Leu	ttc Phe 250	ctg Leu	gtg Val	830

gcc	gtg	cat	gaa	ctg	ggc	cat	gca	ctg	ggc	ttg	gag	cac	tct	aat	gac	878
Ala	Val	His	Glu	Leu	Gly	His	Ala	Leu	Gly	Leu	Glu	His	Ser	Asn	Asp	
		255					260					265				
ccc	agt	gct	atc	atg	gct	ccc	ttc	tac	caa	tac	atg	gag	aca	cac	aac	926
Pro	Ser	Ala	Ile	Met	Ala	Pro	Phe	Tyr	Gln	Tyr	Met	Glu	Thr	His	Asn	
	270					275					280					
ttc	aag	cta	ccg	cag	gac	gat	ctc	cag	ggc	atc	cag	aag	att	tac	gga	974
Phe	Lys	Leu	Pro	Gln	Asp	Asp	Leu	Gln	Gly	Ile	Gln	Lys	Ile	Tyr	Gly	
285					290					295					300	
ccc	cca	gct	gag	cct	ctg	gag	ccc	aca	agg	ccc	ctc	cat	aca	ctc	ccg	1022
Pro	Pro	Ala	Glu	Pro	Leu	Glu	Pro	Thr	Arg	Pro	Leu	His	Thr	Leu	Pro	
				305					310					315		
gtc	cgc	agg	atc	cac	tcg	ccg	tct	gag	agg	aag	cac	gag	cgg	cac	cca	1070
Val	Arg	Arg	Ile	His	Ser	Pro	Ser	Glu	Arg	Lys	His	Glu	Arg	His	Pro	
			320					325					330			
agg	ccc	cca	cgg	ccg	ccc	ctt	ggg	gac	cgg	cca	tcc	act	cca	ggg	gcc	1118
Arg	Pro	Pro	Arg	Pro	Pro	Leu	Gly	Asp	Arg	Pro	Ser	Thr	Pro	Gly	Ala	
		335					340					345				
aaa	ccc	aac	atc	tgc	gat	ggc	aac	ttc	aac	aca	gtg	gcc	ctc	ttc	cga	1166
Lys	Pro	Asn	Ile	Cys	Asp	Gly	Asn	Phe	Asn	Thr	Val	Ala	Leu	Phe	Arg	
		350				355					360					
ggg	gag	atg	ttt	gtg	ttc	aag	gat	cgc	tgg	ttc	tgg	cgc	ctg	cgc	aat	1214
Gly	Glu	Met	Phe	Val	Phe	Lys	Asp	Arg	Trp	Phe	Trp	Arg	Leu	Arg	Asn	
365					370					375					380	
aac	cgg	gtg	cag	gaa	ggc	tac	ccc	atg	cag	atc	gaa	cag	ttc	tgg	aag	1262
Asn	Arg	Val	Gln	Glu	Gly	Tyr	Pro	Met	Gln	Ile	Glu	Gln	Phe	Trp	Lys	
				385					390					395		
ggc	ctg	ccc	gcc	cgc	ata	gac	gca	gcc	tat	gaa	aga	gct	gac	ggg	aga	1310
Gly	Leu	Pro	Ala	Arg	Ile	Asp	Ala	Ala	Tyr	Glu	Arg	Ala	Asp	Gly	Arg	
			400					405					410			
ttc	gtc	ttc	ttc	aaa	gga	gac	aag	tac	tgg	gtt	ttc	aaa	gaa	gtg	acg	1358
Phe	Val	Phe	Phe	Lys	Gly	Asp	Lys	Tyr	Trp	Val	Phe	Lys	Glu	Val	Thr	
		415					420					425				
gtg	gaa	cct	ggg	tac	ccc	cac	agc	ttg	ggg	gag	ctg	gga	agc	tgc	ctg	1406
Val	Glu	Pro	Gly	Tyr	Pro	His	Ser	Leu	Gly	Glu	Leu	Gly	Ser	Cys	Leu	
	430					435					440					
ccc	cgt	gaa	gga	att	gac	aca	gct	ctg	cgc	tgg	gaa	cct	gtg	ggc	aaa	1454
Pro	Arg	Glu	Gly	Ile	Asp	Thr	Ala	Leu	Arg	Trp	Glu	Pro	Val	Gly	Lys	
445					450					455					460	

acc	tac	ttc	ttc	aaa	ggc	gaa	cgg	tac	tgg	cgc	tac	agc	gag	gag	cgg	1502
Thr	Tyr	Phe	Phe	Lys	Gly	Glu	Arg	Tyr	Trp	Arg	Tyr	Ser	Glu	Glu	Arg	
				465					470						475	
cga	gcc	aca	gac	cct	ggc	tac	ccc	aag	ccc	atc	acc	gtg	tgg	aag	ggc	1550
Arg	Ala	Thr	Asp	Pro	Gly	Tyr	Pro	Lys	Pro	Ile	Thr	Val	Trp	Lys	Gly	
			480					485					490			
atc	ccg	cag	gct	ccg	caa	ggg	gcc	ttc	atc	agc	aag	gaa	gga	tat	tac	1598
Ile	Pro	Gln	Ala	Pro	Gln	Gly	Ala	Phe	Ile	Ser	Lys	Glu	Gly	Tyr	Tyr	
		495					500					505				
acc	tac	ttc	tac	aaa	ggc	cgg	gac	tac	tgg	aag	ttt	gac	aac	cag	aaa	1646
Thr	Tyr	Phe	Tyr	Lys	Gly	Arg	Asp	Tyr	Trp	Lys	Phe	Asp	Asn	Gln	Lys	
	510					515					520					
ctg	agc	gtg	gag	cca	ggc	tac	cca	cgc	aac	atc	ctg	cgt	gac	tgg	atg	1694
Leu	Ser	Val	Glu	Pro	Gly	Tyr	Pro	Arg	Asn	Ile	Leu	Arg	Asp	Trp	Met	
525					530				535						540	
ggc	tgc	aag	cag	aag	gag	gta	gag	cgg	cgt	aag	gag	cgg	agg	ctg	ccc	1742
Gly	Cys	Lys	Gln	Lys	Glu	Val	Glu	Arg	Arg	Lys	Glu	Arg	Arg	Leu	Pro	
				545					550					555		
cag	gat	gat	gtg	gac	atc	atg	gtg	acc	atc	gat	gac	gtg	cca	ggc	tct	1790
Gln	Asp	Asp	Val	Asp	Ile	Met	Val	Thr	Ile	Asp	Asp	Val	Pro	Gly	Ser	
			560					565					570			
gtg	aac	gct	gtg	gct	gtg	gtt	gtc	ccc	tgc	aca	ctg	tcc	ctc	tgc	ctc	1838
Val	Asn	Ala	Val	Ala	Val	Val	Val	Pro	Cys	Thr	Leu	Ser	Leu	Cys	Leu	
		575					580					585				
ctg	gtg	ctg	ctc	tac	act	atc	ttc	caa	ttc	aag	aac	aag	gcg	ggg	cct	1886
Leu	Val	Leu	Leu	Tyr	Thr	Ile	Phe	Gln	Phe	Lys	Asn	Lys	Ala	Gly	Pro	
	590					595					600					
cag	ccc	gtc	acc	tac	tat	aag	cgg	ccg	gtc	cag	gag	tgg	gta			1928
Gln	Pro	Val	Thr	Tyr	Tyr	Lys	Arg	Pro	Val	Gln	Glu	Trp	Val			
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Ser Leu Gly Val Glu Trp Leu Ser Arg Phe Gly Tyr Leu Pro Pro Ala
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Asp Glu Ala Thr Leu Ala Leu Met Lys Thr Pro Arg Cys Ser Leu Pro
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Pro Arg Asp Ser Pro Leu Gly Arg Asp Thr Val Arg Ala Leu Met Tyr
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Tyr Ala Leu Lys Val Trp Ser Asp Ile Thr Pro Leu Asn Phe His Glu
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Val Ala Gly Asn Ala Ala Asp Ile Gln Ile Asp Phe Ser Lys Ala Asp
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His Asn Asp Gly Tyr Pro Phe Asp Gly Pro Gly Gly Thr Val Ala His
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Ala Phe Phe Pro Gly Asp His His Thr Ala Gly Asp Thr His Phe Asp
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Asp Asp Glu Pro Trp Thr Phe Arg Ser Ser Asp Ala His Gly Met Asp
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Phe	Phe	Lys	Asp	Gln	Leu	Tyr	Trp	Arg	Tyr	Asp	Asp	His	Thr	Arg	Arg	450	455	460
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Ser	Met	Leu	Asp	Asp	Ala	Met	Arg	Trp	Ser	Asp	Gly	Ala	Ser	Tyr	Phe	485	490	495
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Ala	Pro	Gly	Tyr	Pro	Gln	Ser	Thr	Ala	Arg	Asp	Trp	Leu	Val	Cys	Gly	515	520	525
Glu	Pro	Leu	Ala	Asp	Ala	Glu	Asp	Val	Gly	Pro	Gly	Pro	Gln	Gly	Arg	530	535	540
Ser	Gly	Ala	Gln	Asp	Gly	Leu	Ala	Val	Cys	Ser	Cys	Thr	Ser	Asp	Ala	545	550	555
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 Thr His Phe Asp Asp Asp Glu Ala Trp Thr Phe Arg Ser Ser Asp Ala
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Thr	Leu	Asp	Asp	Ala	Met	Arg	Trp	Ser	Asp	Gly	Ala	Ser	Tyr	Phe	Phe	485	490	495
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Tyr	Glu	Val	Cys	Ser	Cys	Thr	Ser	Gly	Ala	Ser	Ser	Pro	Pro	Gly	Ala	565	570	575
Pro	Gly	Pro	Leu	Val	Ala	Ala	Thr	Met	Leu	Leu	Leu	Leu	Pro	Pro	Leu	580	585	590
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Glu Glu Leu Ser Lys Ala Ile Thr Ala Met Gln Gln Phe Gly Gly
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Ala	Gly	Asp	Thr	His	Phe	Asp	Asp	Asp	Glu	Pro	Trp	Thr	Phe	Arg	Ser	
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Pro	Leu	Trp	Arg	Gly	Val	Pro	Ser	Met	Leu	Asp	Asp	Ala	Met	Arg	Trp	
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Ser	Asp	Gly	Ala	Ser	Tyr	Phe	Phe	Arg	Gly	Gln	Glu	Tyr	Trp	Lys	Val	
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Arg Asp Trp Leu Val Cys Gly Glu Pro Leu Ala Asp Ala Glu Asp Val
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Ala Arg Gly Pro Gly Pro Pro Pro Pro Gly Pro Gly Leu Ser Arg Leu
10 15 20

Arg	Asp	Ser	Pro	Leu	Gly	His	Asp	Thr	Val	Arg	Ala	Leu	Met	Tyr	Tyr	
150					155					160					165	
gcc	ctc	aag	gtc	tgg	agc	gac	att	gcg	ccc	ctg	aac	ttc	cac	gag	gtg	642
Ala	Leu	Lys	Val	Trp	Ser	Asp	Ile	Ala	Pro	Leu	Asn	Phe	His	Glu	Val	
				170					175					180		
gcg	ggc	agc	acc	gcc	gac	atc	cag	atc	gac	ttc	tcc	aag	gcc	gac	cat	690
Ala	Gly	Ser	Thr	Ala	Asp	Ile	Gln	Ile	Asp	Phe	Ser	Lys	Ala	Asp	His	
			185					190					195			
aac	gac	ggc	tac	ccc	ttc	gac	ggc	ccc	ggc	ggc	acc	gtg	gcc	cac	gcc	738
Asn	Asp	Gly	Tyr	Pro	Phe	Asp	Gly	Pro	Gly	Gly	Thr	Val	Ala	His	Ala	
		200					205					210				
ttc	ttc	ccc	ggc	cac	cac	cac	acc	gcc	ggg	gac	acc	cac	ttt	gac	gat	786
Phe	Phe	Pro	Gly	His	His	His	Thr	Ala	Gly	Asp	Thr	His	Phe	Asp	Asp	
		215				220					225					
gac	gag	gcc	tgg	acc	ttc	cgc	tcc	tcg	gat	gcc	cac	ggg	atg	gac	ctg	834
Asp	Glu	Ala	Trp	Thr	Phe	Arg	Ser	Ser	Asp	Ala	His	Gly	Met	Asp	Leu	
230					235					240					245	
ttt	gca	gtg	gct	gtc	cac	gag	ttt	ggc	cac	gcc	att	ggg	tta	agc	cat	882
Phe	Ala	Val	Ala	Val	His	Glu	Phe	Gly	His	Ala	Ile	Gly	Leu	Ser	His	
				250					255					260		
gtg	gcc	gct	gca	cac	tcc	atc	atg	cgg	ccg	tac	tac	cag	ggc	ccg	gtg	930
Val	Ala	Ala	Ala	His	Ser	Ile	Met	Arg	Pro	Tyr	Tyr	Gln	Gly	Pro	Val	
			265					270					275			
ggt	gac	ccg	ctg	cgc	tac	ggg	ctc	ccc	tac	gag	gac	aag	gtg	cgc	gtc	978
Gly	Asp	Pro	Leu	Arg	Tyr	Gly	Leu	Pro	Tyr	Glu	Asp	Lys	Val	Arg	Val	
		280					285					290				
tgg	cag	ctg	tac	ggt	gtg	cgg	gag	tct	gtg	tct	ccc	acg	gcg	cag	ccc	1026
Trp	Gln	Leu	Tyr	Gly	Val	Arg	Glu	Ser	Val	Ser	Pro	Thr	Ala	Gln	Pro	
		295				300					305					
gag	gag	cct	ccc	ctg	ctg	ccg	gag	ccc	cca	gac	aac	cgg	tcc	agc	gcc	1074
Glu	Glu	Pro	Pro	Leu	Leu	Pro	Glu	Pro	Pro	Asp	Asn	Arg	Ser	Ser	Ala	
310					315					320					325	
ccg	ccc	agg	aag	gac	gtg	ccc	cac	aga	tgc	agc	act	cac	ttt	gac	gcg	1122

Pro	Pro	Arg	Lys	Asp	Val	Pro	His	Arg	Cys	Ser	Thr	His	Phe	Asp	Ala	
				330					335					340		
gtg	gcc	cag	atc	cgg	ggt	gaa	gct	ttc	ttc	ttc	aaa	ggc	aag	tac	ttc	1170
Val	Ala	Gln	Ile	Arg	Gly	Glu	Ala	Phe	Phe	Phe	Lys	Gly	Lys	Tyr	Phe	
			345					350					355			
tgg	cgg	ctg	acg	cgg	gac	cgg	cac	ctg	gtg	tcc	ctg	cag	ccg	gca	cag	1218
Trp	Arg	Leu	Thr	Arg	Asp	Arg	His	Leu	Val	Ser	Leu	Gln	Pro	Ala	Gln	
		360					365					370				
atg	cac	cgc	ttc	tgg	cgg	ggc	ctg	ccg	ctg	cac	ctg	gac	agc	gtg	gac	1266
Met	His	Arg	Phe	Trp	Arg	Gly	Leu	Pro	Leu	His	Leu	Asp	Ser	Val	Asp	
	375					380					385					
gcc	gtg	tac	gag	cgc	acc	agc	gac	cac	aag	atc	gtc	ttc	ttt	aaa	gga	1314
Ala	Val	Tyr	Glu	Arg	Thr	Ser	Asp	His	Lys	Ile	Val	Phe	Phe	Lys	Gly	
390					395					400					405	
gac	agg	tac	tgg	gtg	ttc	aag	gac	aat	aac	gta	gag	gaa	gga	tac	ccg	1362
Asp	Arg	Tyr	Trp	Val	Phe	Lys	Asp	Asn	Asn	Val	Glu	Glu	Gly	Tyr	Pro	
			410					415						420		
cgc	ccc	gtc	tcc	gac	ttc	agc	ctc	ccg	cct	ggc	ggc	atc	gac	gct	gcc	1410
Arg	Pro	Val	Ser	Asp	Phe	Ser	Leu	Pro	Pro	Gly	Gly	Ile	Asp	Ala	Ala	
			425					430					435			
ttc	tcc	tgg	gcc	cac	aat	gac	agg	act	tat	ttc	ttt	aag	gac	cag	ctg	1458
Phe	Ser	Trp	Ala	His	Asn	Asp	Arg	Thr	Tyr	Phe	Phe	Lys	Asp	Gln	Leu	
		440					445					450				
tac	tgg	cgc	tac	gat	gac	cac	acg	agg	cac	atg	gac	ccc	ggc	tac	ccc	1506
Tyr	Trp	Arg	Tyr	Asp	Asp	His	Thr	Arg	His	Met	Asp	Pro	Gly	Tyr	Pro	
	455					460					465					
gcc	cag	agc	ccc	ctg	tgg	agg	ggt	gtc	ccc	agc	acg	ctg	gac	gac	gcc	1554
Ala	Gln	Ser	Pro	Leu	Trp	Arg	Gly	Val	Pro	Ser	Thr	Leu	Asp	Asp	Ala	
470					475				480						485	
atg	cgc	tgg	tcc	gac	ggt	gcc	tcc	tac	ttc	ttc	cgt	ggc	cag	gag	tac	1602
Met	Arg	Trp	Ser	Asp	Gly	Ala	Ser	Tyr	Phe	Phe	Arg	Gly	Gln	Glu	Tyr	
				490					495					500		
tgg	aaa	gtg	ctg	gat	ggc	gag	ctg	gag	gtg	gca	ccc	ggg	tac	cca	cag	1650

Trp	Lys	Val	Leu	Asp	Gly	Glu	Leu	Glu	Val	Ala	Pro	Gly	Tyr	Pro	Gln	
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Ser	Thr	Ala	Arg	Asp	Trp	Leu	Val	Cys	Gly	Asp	Ser	Gln	Ala	Asp	Gly	
		520					525					530				
tct	gtg	gct	gcg	ggc	gtg	gac	gcg	gca	gag	ggg	ccc	cgc	gcc	cct	cca	1746
Ser	Val	Ala	Ala	Gly	Val	Asp	Ala	Ala	Glu	Gly	Pro	Arg	Ala	Pro	Pro	
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gga	caa	cat	gac	cag	agc	cgc	tcg	gag	gac	ggt	tac	gag	gtc	tgc	tca	1794
Gly	Gln	His	Asp	Gln	Ser	Arg	Ser	Glu	Asp	Gly	Tyr	Glu	Val	Cys	Ser	
550					555					560					565	
tgc	acc	tct	ggg	gca	tcc	tct	ccc	ccg	ggg	gcc	cca	ggc	cca	ctg	gtg	1842
Cys	Thr	Ser	Gly	Ala	Ser	Ser	Pro	Pro	Gly	Ala	Pro	Gly	Pro	Leu	Val	
				570					575					580		
gcc	acc	atg	ctg	ctg	ctg	ctg	ccg	cca	ctg	tca	cca	ggc	gcc	ctg		1890
Ala	Ala	Thr	Met	Leu	Leu	Leu	Leu	Pro	Pro	Leu	Ser	Pro	Gly	Ala	Leu	
			585					590					595			
tgg	aca	gcg	gcc	cag	gcc	ctg	acg	cta	tgacacacag	cgcgagccca						1937
Trp	Thr	Ala	Ala	Gln	Ala	Leu	Thr	Leu								
		600					605									
tgagaggaca	gaggcgggtgg	gacagcctgg	ccacagaggg	caaggactgt	gccggagtcc											1997
ctgggggagg	tgctggcgcg	ggatgaggac	gggccaccct	ggcaccggaa	ggccagcaga											2057
gggcacggcc	cgccagggct	gggcaggctc	aggtggcaag	gacggagctg	tcccctagt											2117
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cgcaccgccg	ccagcctcct	ccggccctgg	agggagcatc	tcgggctggg	ggcccacccc											2237
tctctgtgcc	ggcgccacca	accccaccca	cactgctgcc	tggtgctccc	gccggcccac											2297
agggcctccg	tccccaggtc	cccagtgggg	cagccctccc	cacagacgag	ccccccacat											2357
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<212> PRT
<213> Mouse

<400> 5

Met Pro Arg Ser Arg Gly Gly Arg Ala Ala Pro Gly Gln Ala Ser Arg
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Trp Ser Gly Trp Arg Ala Pro Gly Arg Leu Leu Pro Leu Leu Pro Ala
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Leu Cys Cys Leu Ala Ala Ala Ala Gly Ala Gly Lys Pro Ala Gly Ala
35 40 45

Asp Ala Pro Phe Ala Gly Gln Asn Trp Leu Lys Ser Tyr Gly Tyr Leu
50 55 60

Leu Pro Tyr Glu Ser Arg Ala Ser Ala Leu His Ser Gly Lys Ala Leu
65 70 75 80

Gln Ser Ala Val Ser Thr Met Gln Gln Phe Tyr Gly Ile Pro Val Thr
85 90 95

Gly Val Leu Asp Gln Thr Thr Ile Glu Trp Met Lys Lys Pro Arg Cys
100 105 110

Gly Val Pro Asp His Pro His Leu Ser Arg Arg Arg Arg Asn Lys Arg
115 120 125

Tyr Ala Leu Thr Gly Gln Lys Trp Arg Gln Lys His Ile Thr Tyr Ser
130 135 140

Ile His Asn Tyr Thr Pro Lys Val Gly Glu Leu Asp Thr Arg Lys Ala
145 150 155 160

Ile Arg Gln Ala Phe Asp Val Trp Gln Lys Val Thr Pro Leu Thr Phe
165 170 175

Glu Glu Val Pro Tyr His Glu Ile Lys Ser Asp Arg Lys Glu Ala Asp
180 185 190

Ile Met Ile Phe Phe Ala Ser Gly Phe His Gly Asp Ser Ser Pro Phe

195

200

205

Asp Gly Glu Gly Gly Phe Leu Ala His Ala Tyr Phe Pro Gly Pro Gly
210 215 220

Ile Gly Gly Asp Thr His Phe Asp Ser Asp Glu Pro Trp Thr Leu Gly
225 230 235 240

Asn Ala Asn His Asp Gly Asn Asp Leu Phe Leu Val Ala Val His Glu
245 250 255

Leu Gly His Ala Leu Gly Leu Glu His Ser Asn Asp Pro Ser Ala Ile
260 265 270

Met Ala Pro Phe Tyr Gln Tyr Met Glu Thr His Asn Phe Lys Leu Pro
275 280 285

Gln Asp Asp Leu Gln Gly Ile Gln Lys Ile Tyr Gly Pro Pro Ala Glu
290 295 300

Pro Leu Glu Pro Thr Arg Pro Leu His Thr Leu Pro Val Arg Arg Ile
305 310 315 320

His Ser Pro Ser Glu Arg Lys His Glu Arg His Pro Arg Pro Pro Arg
325 330 335

Pro Pro Leu Gly Asp Arg Pro Ser Thr Pro Gly Ala Lys Pro Asn Ile
340 345 350

Cys Asp Gly Asn Phe Asn Thr Val Ala Leu Phe Arg Gly Glu Met Phe
355 360 365

Val Phe Lys Asp Arg Trp Phe Trp Arg Leu Arg Asn Asn Arg Val Gln
370 375 380

Glu Gly Tyr Pro Met Gln Ile Glu Gln Phe Trp Lys Gly Leu Pro Ala
385 390 395 400

Arg Ile Asp Ala Ala Tyr Glu Arg Ala Asp Gly Arg Phe Val Phe Phe
405 410 415

Lys Gly Asp Lys Tyr Trp Val Phe Lys Glu Val Thr Val Glu Pro Gly
420 425 430

Tyr Pro His Ser Leu Gly Glu Leu Gly Ser Cys Leu Pro Arg Glu Gly
 435 440 445
 Ile Asp Thr Ala Leu Arg Trp Glu Pro Val Gly Lys Thr Tyr Phe Phe
 450 455 460
 Lys Gly Glu Arg Tyr Trp Arg Tyr Ser Glu Glu Arg Arg Ala Thr Asp
 465 470 475 480
 Pro Gly Tyr Pro Lys Pro Ile Thr Val Trp Lys Gly Ile Pro Gln Ala
 485 490 495
 Pro Gln Gly Ala Phe Ile Ser Lys Glu Gly Tyr Tyr Thr Tyr Phe Tyr
 500 505 510
 Lys Gly Arg Asp Tyr Trp Lys Phe Asp Asn Gln Lys Leu Ser Val Glu
 515 520 525
 Pro Gly Tyr Pro Arg Asn Ile Leu Arg Asp Trp Met Gly Cys Lys Gln
 530 535 540
 Lys Glu Val Glu Arg Arg Lys Glu Arg Arg Leu Pro Gln Asp Asp Val
 545 550 555 560
 Asp Ile Met Val Thr Ile Asp Asp Val Pro Gly Ser Val Asn Ala Val
 565 570 575
 Ala Val Val Val Pro Cys Thr Leu Ser Leu Cys Leu Leu Val Leu Leu
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 Tyr Thr Ile Phe Gln Phe Lys Asn Lys Ala Gly Pro Gln Pro Val Thr
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 Tyr Tyr Lys Arg Pro Val Gln Glu Trp Val
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<400> 6
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Gly	Arg	Leu	Leu	Leu	Leu	Leu	Leu	Pro	Ala	Leu	Cys	Cys	Leu	Pro	Gly			
		35					40					45						
Ala	Ala	Arg	Ala	Ala	Ala	Ala	Ala	Ala	Gly	Ala	Gly	Asn	Arg	Ala	Ala			
		50					55					60						
Val	Ala	Val	Ala	Val	Ala	Arg	Ala	Asp	Glu	Ala	Glu	Ala	Pro	Phe	Ala			
		65			70					75					80			
Gly	Gln	Asn	Trp	Leu	Lys	Ser	Tyr	Gly	Tyr	Leu	Leu	Pro	Tyr	Asp	Ser			
				85					90					95				
Arg	Ala	Ser	Ala	Leu	His	Ser	Ala	Lys	Ala	Leu	Gln	Ser	Ala	Val	Ser			
			100					105					110					
Thr	Met	Gln	Gln	Phe	Tyr	Gly	Ile	Pro	Val	Thr	Gly	Val	Leu	Asp	Gln			
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Thr	Thr	Ile	Glu	Trp	Met	Lys	Lys	Pro	Arg	Cys	Gly	Val	Pro	Asp	His			
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Pro	His	Leu	Ser	Arg	Arg	Arg	Arg	Asn	Lys	Arg	Tyr	Ala	Leu	Thr	Gly			
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Gln	Lys	Trp	Arg	Gln	Lys	His	Ile	Thr	Tyr	Ser	Ile	His	Asn	Tyr	Thr			
				165					170					175				
Pro	Lys	Val	Gly	Glu	Leu	Asp	Thr	Arg	Lys	Ala	Ile	Arg	Gln	Ala	Phe			
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Asp	Val	Trp	Gln	Lys	Val	Thr	Pro	Leu	Thr	Phe	Glu	Glu	Val	Pro	Tyr			
		195					200					205						
His	Glu	Ile	Lys	Ser	Asp	Arg	Lys	Glu	Ala	Asp	Ile	Met	Ile	Phe	Phe			
	210					215					220							
Ala	Ser	Gly	Phe	His	Gly	Asp	Ser	Ser	Pro	Phe	Asp	Gly	Glu	Gly	Gly			
225					230					235					240			
Phe	Leu	Ala	His	Ala	Tyr	Phe	Pro	Gly	Pro	Gly	Ile	Gly	Gly	Asp	Thr			
				245					250					255				

His Phe Asp Ser Asp Glu Pro Trp Thr Leu Gly Asn Ala Asn His Asp
 260 265 270
 Gly Asn Asp Leu Phe Leu Val Ala Val His Glu Leu Gly His Ala Leu
 275 280 285
 Gly Leu Glu His Ser Ser Asp Pro Ser Ala Ile Met Ala Pro Phe Tyr
 290 295 300
 Gln Tyr Met Glu Thr His Asn Phe Lys Leu Pro Gln Asp Asp Leu Gln
 305 310 315 320
 Gly Ile Gln Lys Ile Tyr Gly Pro Pro Ala Glu Pro Leu Glu Pro Thr
 325 330 335
 Arg Pro Leu Pro Thr Leu Pro Val Arg Arg Ile His Ser Pro Ser Glu
 340 345 350
 Arg Lys His Glu Arg Gln Pro Arg Pro Pro Arg Pro Pro Leu Gly Asp
 355 360 365
 Arg Pro Ser Thr Pro Gly Thr Lys Pro Asn Ile Cys Asp Gly Asn Phe
 370 375 380
 Asn Thr Val Ala Leu Phe Arg Gly Glu Met Phe Val Phe Lys Asp Arg
 385 390 395 400
 Trp Phe Trp Arg Leu Arg Asn Asn Arg Val Gln Glu Gly Tyr Pro Met
 405 410 415
 Gln Ile Glu Gln Phe Trp Lys Gly Leu Pro Ala Arg Ile Asp Ala Ala
 420 425 430
 Tyr Glu Arg Ala Asp Gly Arg Phe Val Phe Phe Lys Gly Asp Lys Tyr
 435 440 445
 Trp Val Phe Lys Glu Val Thr Val Glu Pro Gly Tyr Pro His Ser Leu
 450 455 460
 Gly Glu Leu Gly Ser Cys Leu Pro Arg Glu Gly Ile Asp Thr Ala Leu
 465 470 475 480
 Arg Trp Glu Pro Val Gly Lys Thr Tyr Phe Phe Lys Gly Glu Arg Tyr
 485 490 495

Trp Arg Tyr Ser Glu Glu Arg Arg Ala Thr Asp Pro Gly Tyr Pro Lys
500 505 510

Pro Ile Thr Val Trp Lys Gly Ile Pro Gln Ala Pro Gln Gly Ala Phe
515 520 525

Ile Ser Lys Glu Gly Tyr Tyr Thr Tyr Phe Tyr Lys Gly Arg Asp Tyr
530 535 540

Trp Lys Phe Asp Asn Gln Lys Leu Ser Val Glu Pro Gly Tyr Pro Arg
545 550 555 560

Asn Ile Leu Arg Asp Trp Met Gly Cys Asn Gln Lys Glu Val Glu Arg
565 570 575

Arg Lys Glu Arg Arg Leu Pro Gln Asp Asp Val Asp Ile Met Val Thr
580 585 590

Ile Asn Asp Val Pro Gly Ser Val Asn Ala Val Ala Val Val Ile Pro
595 600 605

Cys Ile Leu Ser Leu Cys Ile Leu Val Leu Val Tyr Thr Ile Phe Gln
610 615 620

Phe Lys Asn Lys Thr Gly Pro Gln Pro Val Thr Tyr Tyr Lys Arg Pro
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Val Gln Glu Trp Val
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<212> DNA

<213> Mouse

<220>

<221> CDS

<222> (75)..(1928)

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Met Pro Arg Ser Arg Gly Gly Arg Ala Ala Pro Gly

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cag gcc tcg cgc tgg agc ggc tgg cgg gcc ccg ggg cgg ctg ctg ccg	158														
Gln Ala Ser Arg Trp Ser Gly Trp Arg Ala Pro Gly Arg Leu Leu Pro															
15 20 25															
ctg ctg ccc gcg ctc tgc tgc ctc gcg gcg gcg gcg ggg gcc ggg aag	206														
Leu Leu Pro Ala Leu Cys Cys Leu Ala Ala Ala Ala Gly Ala Gly Lys															
30 35 40															
ccg gcc ggg gcg gac gcg ccc ttc gct ggg cag aac tgg tta aaa tca	254														
Pro Ala Gly Ala Asp Ala Pro Phe Ala Gly Gln Asn Trp Leu Lys Ser															
45 50 55 60															
tat ggc tat ctg ctt ccc tat gag tgc cgg gca tct gcg ttg cat tct	302														
Tyr Gly Tyr Leu Leu Pro Tyr Glu Ser Arg Ala Ser Ala Leu His Ser															
65 70 75															
ggg aag gcc ttg cag tcc gcg gtc tcc act atg cag cag ttt tac ggg	350														
Gly Lys Ala Leu Gln Ser Ala Val Ser Thr Met Gln Gln Phe Tyr Gly															
80 85 90															
atc cca gtc acc ggt gtg ttg gat cag aca aca atc gag tgg atg aag	398														
Ile Pro Val Thr Gly Val Leu Asp Gln Thr Thr Ile Glu Trp Met Lys															
95 100 105															
aaa cct cga tgt ggc gtc cct gat cat ccc cac ttg agc agg agg agg	446														
Lys Pro Arg Cys Gly Val Pro Asp His Pro His Leu Ser Arg Arg Arg															
110 115 120															
aga aat aag cga tat gcc cta act gga cag aag tgg agg cag aaa cac	494														
Arg Asn Lys Arg Tyr Ala Leu Thr Gly Gln Lys Trp Arg Gln Lys His															
125 130 135 140															
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Ile Thr Tyr Ser Ile His Asn Tyr Thr Pro Lys Val Gly Glu Leu Asp															
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aca cgg aag gct att cgt cag gct ttc gat gtg tgg cag aag gtg act	590														
Thr Arg Lys Ala Ile Arg Gln Ala Phe Asp Val Trp Gln Lys Val Thr															
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cca ctg acc ttt gaa gag gtg cca tac cat gag atc aaa agt gac cgg	638														
Pro Leu Thr Phe Glu Glu Val Pro Tyr His Glu Ile Lys Ser Asp Arg															

175

180

185

aag gag gca gac atc atg atc ttc ttt gct tct ggt ttc cat ggt gac 686
 Lys Glu Ala Asp Ile Met Ile Phe Phe Ala Ser Gly Phe His Gly Asp
 190 195 200

agc tcc cca ttt gat ggg gaa ggg gga ttc cta gcc cat gcc tac ttt 734
 Ser Ser Pro Phe Asp Gly Glu Gly Gly Phe Leu Ala His Ala Tyr Phe
 205 210 215 220

cct ggc cca ggg atc gga gga gac act cac ttt gat tca gat gaa ccc 782
 Pro Gly Pro Gly Ile Gly Gly Asp Thr His Phe Asp Ser Asp Glu Pro
 225 230 235

tgg acg cta gga aat gcc aac cat gat ggc aat gac ctc ttc ctg gtg 830
 Trp Thr Leu Gly Asn Ala Asn His Asp Gly Asn Asp Leu Phe Leu Val
 240 245 250

gac gtg cat gaa ctg ggc cat gca ctg ggc ttg gag cac tct aat gac 878
 Ala Val His Glu Leu Gly His Ala Leu Gly Leu Glu His Ser Asn Asp
 255 260 265

ccc agt gct atc atg gct ccc ttc tac caa tac atg gag aca cac aac 926
 Pro Ser Ala Ile Met Ala Pro Phe Tyr Gln Tyr Met Glu Thr His Asn
 270 275 280

ttc aag cta ccg cag gac gat ctc cag ggc atc cag aag att tac gga 974
 Phe Lys Leu Pro Gln Asp Asp Leu Gln Gly Ile Gln Lys Ile Tyr Gly
 285 290 295 300

ccc cca gct gag cct ctg gag ccc aca agg ccc ctc cat aca ctc ccg 1022
 Pro Pro Ala Glu Pro Leu Glu Pro Thr Arg Pro Leu His Thr Leu Pro
 305 310 315

gtc cgc agg atc cac tcg ccg tct gag agg aag cac gag cgg cac cca 1070
 Val Arg Arg Ile His Ser Pro Ser Glu Arg Lys His Glu Arg His Pro
 320 325 330

agg ccc cca cgg ccg ccc ctt ggg gac cgg cca tcc act cca ggt gcc 1118
 Arg Pro Pro Arg Pro Pro Leu Gly Asp Arg Pro Ser Thr Pro Gly Ala
 335 340 345

aaa ccc aac atc tgc gat ggc aac ttc aac aca gtg gcc ctc ttc cga 1166
 Lys Pro Asn Ile Cys Asp Gly Asn Phe Asn Thr Val Ala Leu Phe Arg

350		355		360	
ggg gag atg ttt gtg ttc aag gat cgc tgg ttc tgg cgc ctg cgc aat	1214				
Gly Glu Met Phe Val Phe Lys Asp Arg Trp Phe Trp Arg Leu Arg Asn					
365		370		375	380
aac cgg gtg cag gaa ggc tac ccc atg cag atc gaa cag ttc tgg aag	1262				
Asn Arg Val Gln Glu Gly Tyr Pro Met Gln Ile Glu Gln Phe Trp Lys					
		385		390	395
ggc ctg ccc gcc cgc ata gac gca gcc tat gaa aga gct gac ggg aga	1310				
Gly Leu Pro Ala Arg Ile Asp Ala Ala Tyr Glu Arg Ala Asp Gly Arg					
		400		405	410
ttc gtc ttc ttc aaa gga gac aag tac tgg gtt ttc aaa gaa gtg acg	1358				
Phe Val Phe Phe Lys Gly Asp Lys Tyr Trp Val Phe Lys Glu Val Thr					
		415		420	425
gtg gaa cct ggg tac ccc cac agc ttg ggg gag ctg gga agc tgc ctg	1406				
Val Glu Pro Gly Tyr Pro His Ser Leu Gly Glu Leu Gly Ser Cys Leu					
		430		435	440
ccc cgt gaa gga att gac aca gct ctg cgc tgg gaa cct gtg ggc aaa	1454				
Pro Arg Glu Gly Ile Asp Thr Ala Leu Arg Trp Glu Pro Val Gly Lys					
		445		450	455
acc tac ttc ttc aaa ggc gaa cgg tac tgg cgc tac agc gag gag cgg	1502				
Thr Tyr Phe Phe Lys Gly Glu Arg Tyr Trp Arg Tyr Ser Glu Glu Arg					
		465		470	475
cga gcc aca gac cct ggc tac ccc aag ccc atc acc gtg tgg aag ggc	1550				
Arg Ala Thr Asp Pro Gly Tyr Pro Lys Pro Ile Thr Val Trp Lys Gly					
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atc ccg cag gct ccg caa ggg gcc ttc atc agc aag gaa gga tat tac	1598				
Ile Pro Gln Ala Pro Gln Gly Ala Phe Ile Ser Lys Glu Gly Tyr Tyr					
		495		500	505
acc tac ttc tac aaa ggc cgg gac tac tgg aag ttt gac aac cag aaa	1646				
Thr Tyr Phe Tyr Lys Gly Arg Asp Tyr Trp Lys Phe Asp Asn Gln Lys					
		510		515	520
ctg agc gtg gag cca ggc tac cca cgc aac atc ctg cgt gac tgg atg	1694				
Leu Ser Val Glu Pro Gly Tyr Pro Arg Asn Ile Leu Arg Asp Trp Met					

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Gly Cys Lys Gln Lys Glu Val Glu Arg Arg Lys Glu Arg Arg Leu Pro				
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Gln Asp Asp Val Asp Ile Met Val Thr Ile Asp Asp Val Pro Gly Ser				
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Val Asn Ala Val Ala Val Val Val Pro Cys Thr Leu Ser Leu Cys Leu				
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Leu Val Leu Leu Tyr Thr Ile Phe Gln Phe Lys Asn Lys Ala Gly Pro				
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